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NEW APPLICATIONS OF ORGANOMETALLIC REAGENTS IN
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SYNTHESIS OF α -SANTALOL.

Harvard University, Ph.D., 1972
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NEW APPLICATIONS OF ORGANOMETALLIC REAGENTS IN ORGANIC SYNTHESIS
A STEREOSPECIFIC TOTAL SYNTHESIS OF α -SANTALOL

A thesis presented

by

Herbert Andrew Kirst

to

The Department of Chemistry

in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

in the subject of

Chemistry

Harvard University

Cambridge, Massachusetts

November, 1971

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I am grateful to Professor E. J. Corey for the direction and assistance which he has provided during the course of this work. His wealth of ideas and his interest in research have stimulated and aided this work and aroused my interest in a number of areas of chemistry. It has been a rewarding educational experience to work with Professor Corey.

I wish to thank the numerous graduate students and postdoctoral fellows with whom I have had many helpful discussions; the assistance and information which they have provided has been invaluable. I would especially like to thank John A. Katzenellenbogen and Louis S. Hegedus for their interest in this work and their willingness to share their expertise.

Special thanks are due to Mrs. Louise Hersey, who kindly typed the experimental sections of this thesis.

I also wish to thank the National Science Foundation for predoctoral fellowships and Harvard University for a research assistantship.

PREFACE

The development of reagents and procedures useful for isoprene synthesis is described in the first part of this thesis. In chapter 1, the synthetic utility of a novel, position-specific propargylating agent, lithio-1-trimethylsilylpropyne, is explored. In chapter 2, a stereospecific total synthesis of α -santalol is reported, for which a stereo- and position-specific reduction of a propargylic alcohol was developed. Some new applications of nickel carbonyl in organic synthesis are described in the second part of this thesis. Intramolecular allylic coupling is employed as a new route to macrocyclic lactones. The conversion of diallylic sulfates to 1,5-hexadienes and the conjugate addition to enones by some anionic acylnickel complexes are also studied.

LIST OF ABBREVIATIONS

The following abbreviations are commonly used throughout this thesis.

TMED	N,N,N',N'-Tetramethylethylenediamine
DABCO	1,4-Diazabicyclo[2.2.2]octane
BSA	N,O-Bis(trimethylsilyl)acetamide
COD	1,5-Cyclooctadiene
$i\text{-Bu}_2\text{AlH}$	Diisobutylaluminum hydride
LiAlH_4	Lithium aluminum hydride
BH_3	Borane
HMPA	Hexamethylphosphoric triamide
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
THF	Tetrahydrofuran
DME	1,2-Dimethoxyethane
TG	Tetraethyleneglycol dimethyl ether (tetraglyme)
Me_3Si	Trimethylsilyl-
THP ether	Tetrahydropyranyl ether
mesyl	Methanesulfonyl
pet.ether	30-60° Petroleum ether
\emptyset	Phenyl
Me, Et, Bu	Methyl, ethyl, butyl, etc.

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PART I
SYNTHESIS OF TRISUBSTITUTED OLEFINS

GENERAL INTRODUCTION

Although the structures of many terpenes containing a functionalized isoprene unit $[-C-CH=C(CH_3)-C-]$ ¹ have been known for a long time,² procedures were not developed until recently for stereospecifically constructing the trisubstituted double bonds characteristic of these molecules. Many commonly used methods for constructing olefins, which may generate 1,2-disubstituted double bonds stereoselectively, show little if any stereoselectivity for the generation of trisubstituted double bonds.³ During the last few years, however, the stereospecific synthesis of trisubstituted olefins has been actively investigated by several research groups, and a wide variety of new synthetic procedures have now been reported.^{3,4}

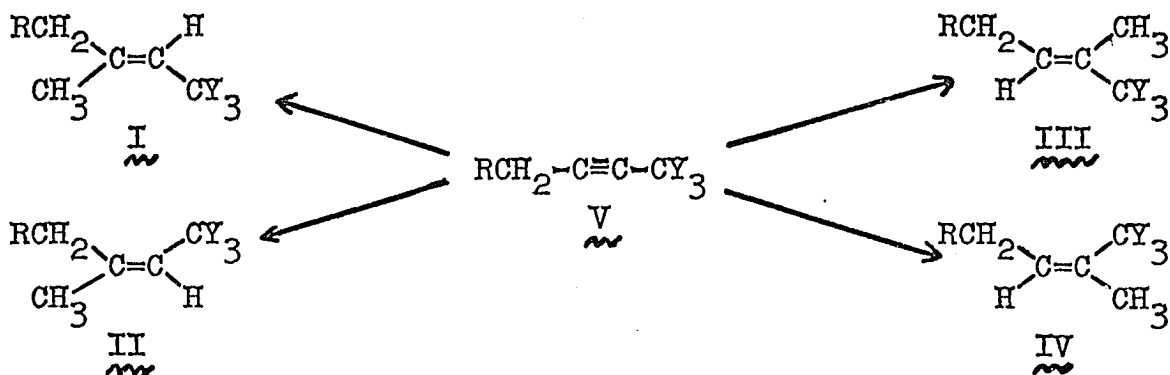
Terpenes containing an oxygenated isoprenoid synthon may be conveniently classified as one of the four possible position- and stereoisomers depicted below ($CY_3 = CH_2OH, CHO, \text{ or } COOH$).

(1) Such a distinct structural unit which can conceivably be introduced into a molecule by some set of reactions has been defined as a synthon; see E. J. Corey, Pure Appl. Chem., 14, 19 (1967).

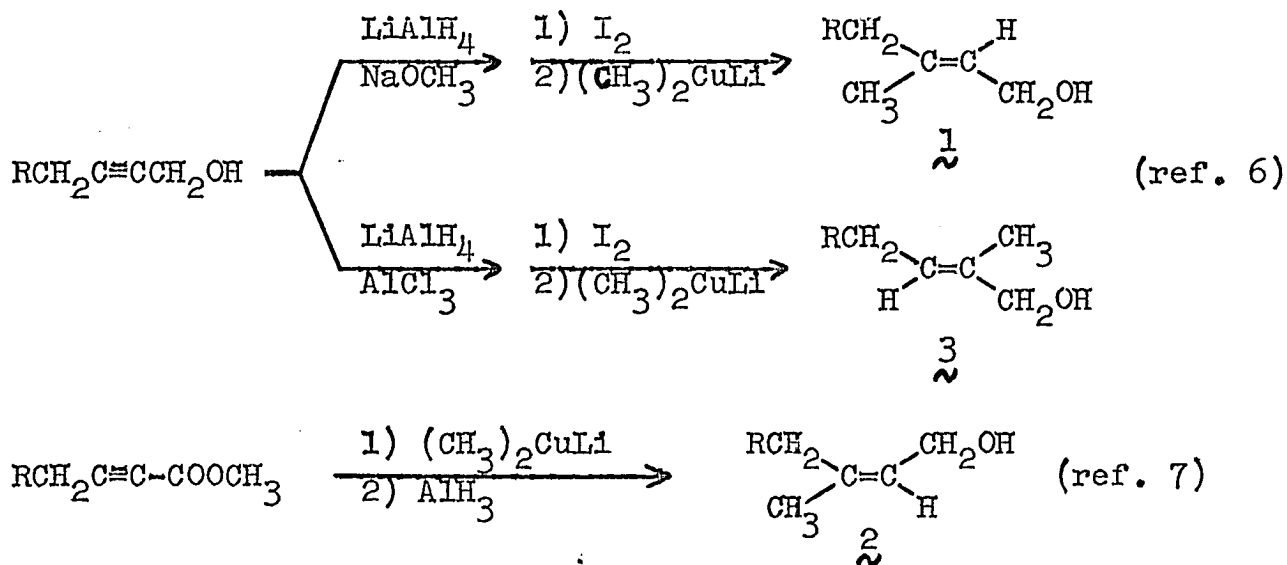
(2) J. L. Simonsen, D. H. R. Barton, W. C. J. Ross, and L. N. Owen, "The Terpenes," 5 volumes, Cambridge University Press, Cambridge, England.

(3) For a detailed discussion of the stereoselectivity observed in reactions available for trisubstituted olefin synthesis prior to 1970, see J. A. Katzenellenbogen, Ph.D. Thesis, Harvard University, August, 1969, chapter 1.

(4) For recent reviews of stereoselective syntheses of trisubstituted olefins, see (a) D. J. Faulkner, Synthesis, 175 (1971); (b) J. Reucroft and P. G. Sammes, Quart. Rev. (London), 25, 135 (1971).



One approach to the synthesis of all four structural types from a common precursor is stereo- and regiospecific⁵ reductions of the triple bond of V, in which the polar functional group (CY₃) can be utilized to control the mode of addition to the triple bond. Such syntheses of allylic alcohols 1, 2, and 3 from propargylic alcohols or propiolic esters have already

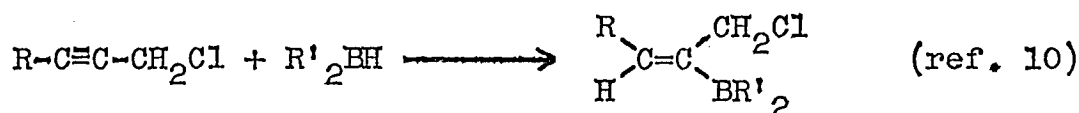
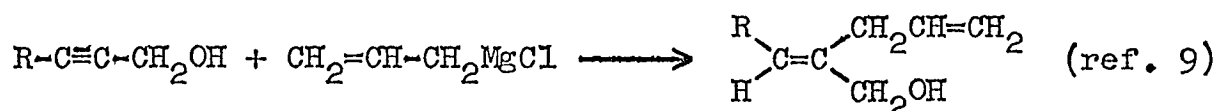
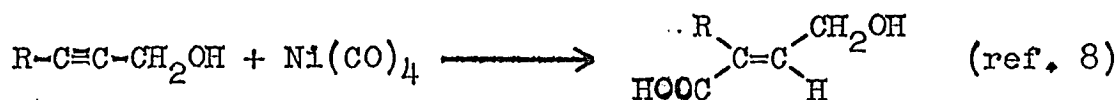


(5) A. Hassner, J. Org. Chem., 33, 2684 (1968).

(6) (a) E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, J. Amer. Chem. Soc., 89, 4245 (1967); (b) E. J. Corey, J. A. Katzenellenbogen, S. A. Roman, and N. W. Gilman, Tetrahedron Lett., 1821 (1971); (c) Reference 3, chapter 2.

(7) (a) E. J. Corey and J. A. Katzenellenbogen, J. Amer. Chem. Soc., 91, 1851 (1969); (b) J. B. Siddall, M. Biskup, and J. H. Fried, ibid., 91, 1853 (1969); (c) J. Klein and R. M. Turkel, ibid., 91, 6186 (1969); (d) Reference 3, chapter 3.

been accomplished.^{6,7} Several other examples of stereospecific addition of organometallic reagents to the triple bond of \underline{V} are known, indicating that this approach is a general one which may be conveniently employed for the synthesis of a variety of substituted allylic alcohols and



carbonyl compounds.¹¹ In chapter two of this thesis, a procedure for the conversion of propargylic alcohols to trisubstituted olefins of type IV is reported, in which the

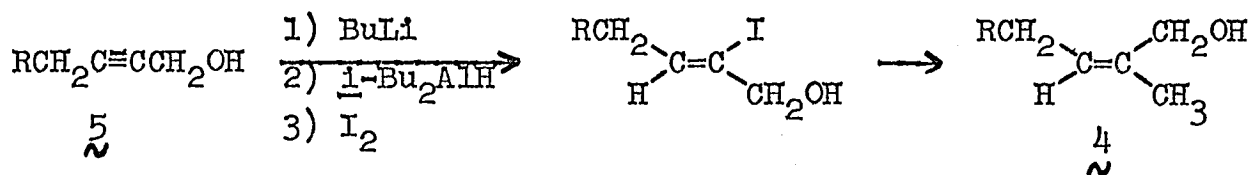
(8) E. R. H. Jones, T. Y. Shen, and M. C. Whiting, J. Chem. Soc., 48 (1951); Y. Yukawa, T. Hanafusa, and K. Fujita, Bull. Chem. Soc. Japan, 37, 158 (1964).

(9) H. G. Richey, Jr. and F. W. von Rein, J. Organometal. Chem., 20, P32 (1969); analogous additions to propargylic amines have been reported: H. G. Richey, Jr., W. F. Erickson, and A. S. Heyn, Tetrahedron Lett., 2183 (1971); for tertiary propargylic alcohols, see J. J. Eisch and J. H. Merkley, J. Organometal. Chem., 20, P27 (1969).

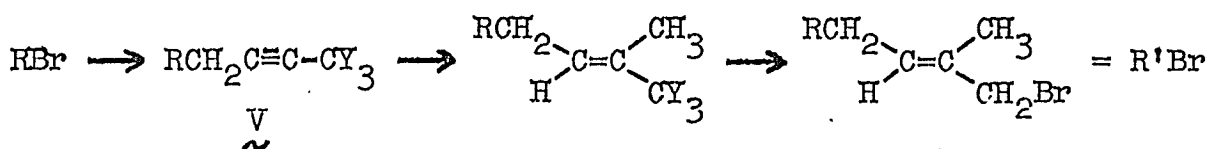
(10) G. Zweifel, A. Horng, and J. T. Snow, J. Amer. Chem. Soc., 92, 1427 (1970).

(11) Some non-stereospecific additions have also been reported. (a) J. F. Normant and M. Bourgain, Tetrahedron Lett., 2583 (1971); (b) J. Tsuji and T. Nogi, J. Org. Chem. 31, 2641 (1966).

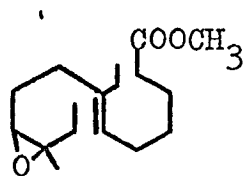
key step is a stereo- and regiospecific addition of diisobutylaluminum hydride to the triple bond of the lithium salt of a propargylic alcohol.



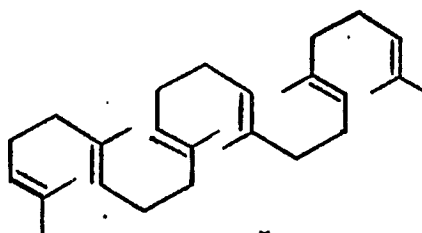
The utility of these triple bond reductions in isoprenoid synthesis would be greatly extended if a convenient method were available for preparing the precursor \sim from any alkyl halide since this would establish a general method for



attaching an isoprenoid unit to a carbon skeleton. Furthermore, such a sequence could be repetitiously applied to assemble polyisoprene compounds such as Cecropia juvenile hormone¹² or structurally-modified squalene molecules.¹³



juvenile hormone



squalene

(12) For recent reviews of syntheses of juvenile hormone, see (a) B. M. Trost, Acc. Chem. Res., **3**, 120 (1970); (b) Y. S. Tsizin and A. A. Drabkina, Russ. Chem. Rev., **39**, 498 (1970); (c) H. Yamamoto, Ph.D. Thesis, Harvard University, April, 1971, pp 73-89; (d) Reference 3, chapter 5.

(13) For discussions of cyclizations of polyolefins, see, for enzymatic cyclizations, reference 11c, part 1, and E. E. van Tamelen, Acc. Chem. Res., **1**, 111 (1968); for chemically-induced cyclizations, see W. S. Johnson, ibid., **1**, 1 (1968).

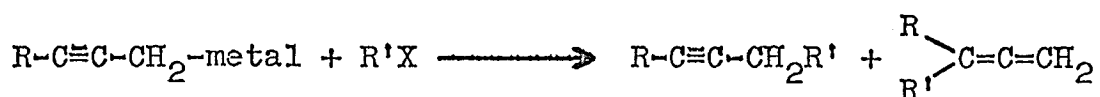
In part one of this thesis, a general procedure for connecting an isoprenoid unit to a carbon skeleton is described, for which a novel reagent, lithio-1-trimethylsilylpropyne, was developed. The new methods developed for isoprenoid synthesis were then utilized for a stereospecific total synthesis of α -santalol, a major constituent of East Indian sandalwood oil.

CHAPTER 1

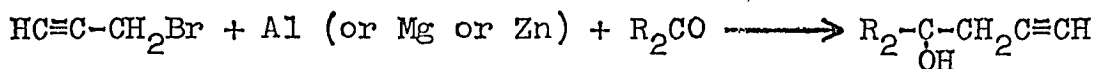
GENERATION AND UTILIZATION OF LITHIO-1-TRIMETHYLSILYLPROPYNONE

A. Survey of Some Propargylic Organometallic Reagents.¹⁴

Formation of a single isomer from reactions of ambident reagents is often difficult to achieve. For example, propargylic organometallic compounds may yield both acetylenic and allenic products.



It now appears well-established that the addition of propargylmagnesium and propargylaluminum compounds to aldehydes and ketones produces exclusively acetylenic alcohols;¹⁵ propargylaluminum bromide is generally preferred because formation of 1,5-hexadiyne is minimal and high yields of alcohols are reproducibly obtained.¹⁶ Propargylzinc bromide

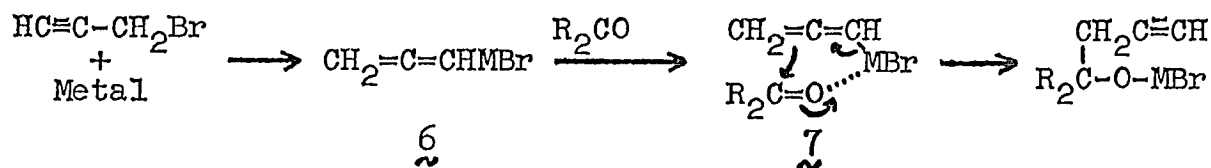


(14) In this thesis, organometallic reagents derived from propargyl bromide or propyne will be consistently called propargylic compounds; the use of this term is not intended to suggest any particular structure.

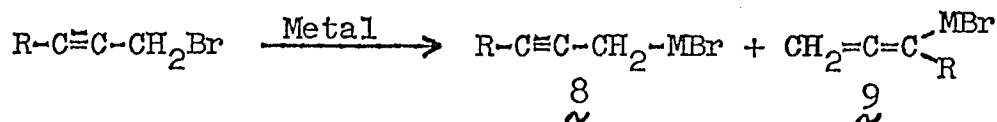
(15) (a) M. Gaudemar, Ann. Chim. (Paris), 161 (1956); (b) H. Gutmann, O. Isler, G. Ryser, P. Zeller, and B. Pellmont, Helv. Chim. Acta, 42, 719 (1959); (c) F. Sondheimer, Y. Amiel, and Y. Gaoni, J. Amer. Chem. Soc., 84, 270 (1962); (d) D. F. Schneider and B. C. L. Weedon, J. Chem. Soc., Sect. C, 1686 (1967).

(16) (a) L. Miginiac-Groizeleau, Ann. Chim. (Paris), 1071 (1961); (b) P. Lauger, M. Prost, and R. Charlier, Helv. Chim. Acta, 42, 2379 (1959); (c) M. L. Capmau, W. Chodkiewicz, and P. Cadot, Tetrahedron Lett., 1619 (1965).

has also been employed;¹⁷ although mixtures of acetylenic and allenic alcohols are often obtained, the latter have been shown to arise in some cases from isomerization of the initially-formed acetylenic alkoxides and were eliminated by operating at -10° .¹⁸ The regioselectivity observed in these additions has been explained by a cyclic transition state (7) in which addition to the carbonyl group occurs by rearrangement (propargylic transposition) of an allenyl organometallic compound (6)¹⁹ coordinated to the carbonyl oxygen atom.²⁰



For organometallic derivatives of 1-substituted propargylic bromides, the propargylic and allenic tautomers (8 and 9) have comparable energies and both species are present in solution;



(17) (a) W. D. Celmer and I. A. Solomons, J. Amer. Chem. Soc., 75, 3430 (1953); (b) L. Crombie and A. G. Jacklin, J. Chem. Soc., 1740 (1955); (c) M. Gaudemar and S. Travers, C. R. Acad. Sci., Paris, Ser. C, 262, 139 (1966).

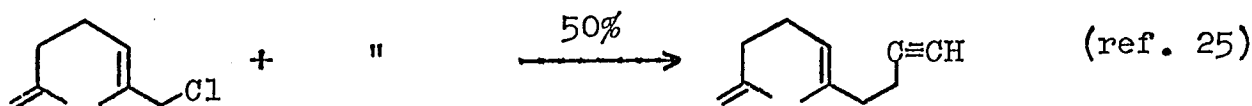
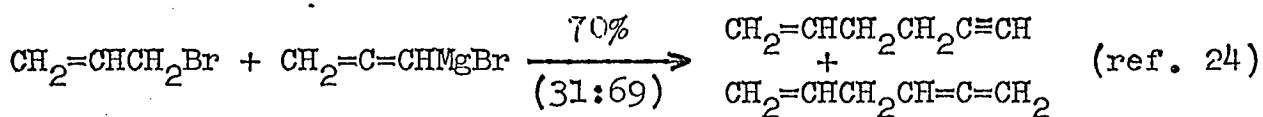
(18) M. Gaudemar, Bull. Soc. Chim. France, 974 (1962).

(19) The allenic structure of these reagents has been established from their infrared spectra: C. Prévost, M. Gaudemar, L. Miginiac, F. Bardone-Gaudemar, and M. Andrac, ibid., 679 (1959).

(20) For detailed discussions of this mechanism, see M. Gaudemar, ibid., 1475 (1963) and M. Andrac, F. Gaudemar, M. Gaudemar, B. Gross, L. Miginiac, P. Miginiac, and C. Prévost, ibid., 1385 (1963) as well as reference 19.

as expected, addition of a carbonyl compound leads to a mixture of acetylenic and allenic alcohols.^{21,22}

Unfortunately, propargyl-magnesium, -aluminum, and -zinc compounds are either unreactive or react in a non-regiospecific manner with most functional groups other than aldehydes and ketones. The examples shown below illustrate the lack of specificity generally found in reactions with alkyl halides.²³



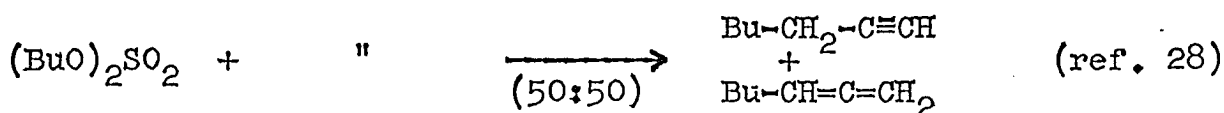
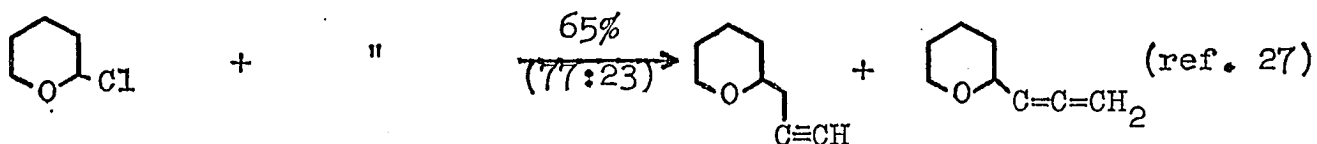
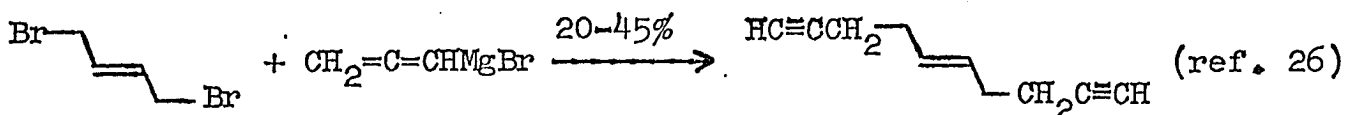
(21) M. Gaudemar, C. R. Acad. Sci., Paris, 254, 1100 (1962) and references 18 and 19.

(22) In accord with steric considerations, secondary and tertiary propargylic bromides yield exclusively allenyl Grignard reagents and acetylenic alcohols: Y. Pasternak, C. R. Acad. Sci., Paris, 255, 1750 (1962); see also reference 18.

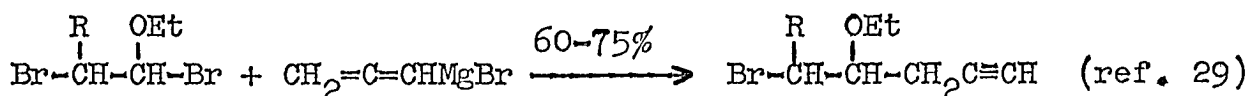
(23) Other functional groups examined include (a) esters: M. Gaudemar and R. Couffignal, C. R. Acad. Sci., Paris, Ser. C, 265, 42 (1967); (b) carbonates: G. Peiffer and H. Driguez, ibid., 267, 773 (1968); (c) carbon dioxide: J. H. Wotiz, J. S. Matthews, and J. A. Lieb, J. Amer. Chem. Soc., 73, 5503 (1951); (d) tertiary amides: F. Gaudemar-Bardone, Ann. Chim. (Paris), 52 (1958); (e) orthoesters: Y. Pasternak and J-C. Traynard, Bull. Soc. Chim. France, 356 (1966); (f) nitriles: references 16a and 20a.

(24) L. Groizeleau-Miginiac, C. R. Acad. Sci., Paris, 248, 1190 (1959).

(25) (a) W. S. Johnson, T. Li, C. A. Harbert, W. R. Bartlett, T. R. Herrin, B. Staskum, and D. H. Rich, J. Amer. Chem. Soc., 92, 4461 (1970); (b) for analogous results with other allylic halides, see P. A. Stadler, A. Nechvatal, A. J. Frey, and A. Eschenmoser, Hely. Chim. Acta, 40, 1373 (1957) and K. E. Harding and K. A. Parker, Tetrahedron Lett., 1633 (1971).



It has recently been shown that isolation of the desired acetylene from the reaction mixture may be facilitated by its conversion to a 1-trimethylsilylacetylene, purification, and desilylation.^{25a,26b} Regiospecific alkylation has been observed, however, with relatively hindered alkyl halides; in these cases, the staggered conformation (VI) of the acetylenic product may be especially favored over the partially eclipsed conformation (VII) of the allenic product.

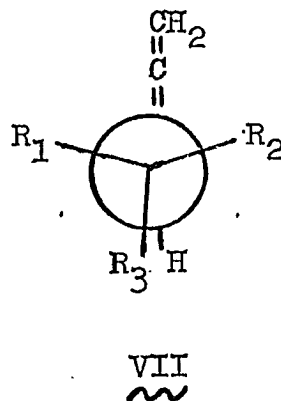
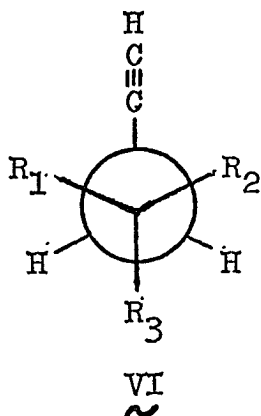
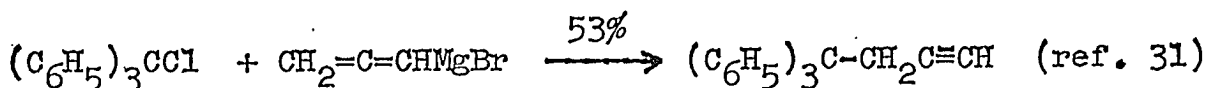
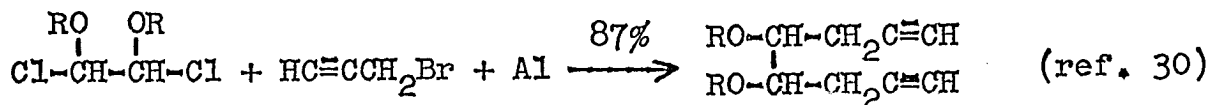


(26) (a) F. Sondheimer, R. Wolovsky, and D. A. Ben-Efraim, J. Amer. Chem. Soc., **83**, 1686 (1961); (b) see also R. E. Ireland, M. I. Dawson, and C. A. Lipinski, Tetrahedron Lett., 2247 (1970).

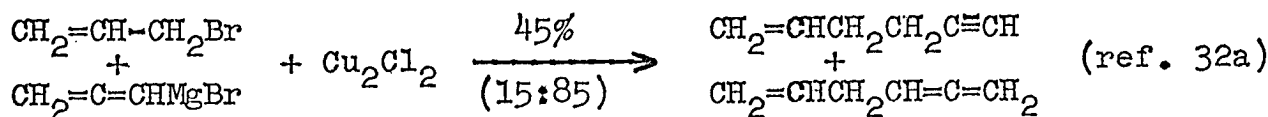
(27) L. Gouin, M-C. Faroux, and O. Riobé, Bull. Soc. Chim. France, 2320 (1966)

(28) M. Gaudemar, C. R. Acad. Sci., Paris, **243**, 1216 (1956).

(29) M. Bertrand, ibid., **244**, 619 (1957); analogous results reported in reference 16a.



Alkylation of propargylmagnesium bromide in the presence of cuprous salts has been shown to moderately increase the proportion of allenic product.³² Cuprous bromide is also



known to catalyze the isomerization of propargyl bromide to allenyl bromide³³ and the conversion of propargylic halides

(30) H-J. Kabbe, E. Truscheit, and K. Eiter, Ann. Chem., 684, 14 (1965).

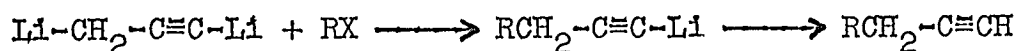
(31) J-C. Masson, M. L. Quan, and P. Cadiot, Bull. Soc. Chim. France, 777 (1967).

(32) (a) G. Peiffer, Bull. Soc. Chim. France, 776 (1962); (b) see also P. Perriot and M. Gaudemar, C. R. Acad. Sci., Paris, Ser. C, 272, 698 (1971) and reference 26a.

(33) (a) Y. Pasternak and G. Peiffer, C. R. Acad. Sci., Paris, 259, 1142 (1964); (b) M. Gaudemar, ibid., 258, 4803 (1964).

to allenic nitriles.^{33a,34} Although the species involved in these transformations have not been investigated, it seems likely that propargylcopper complexes are involved.

Alkali metal carbanions are more reactive alkylating agents than Grignard reagents, but formation of propargyl-lithium complexes in a manner analogous to propargylmagnesium complexes is prohibited by the acidity of the acetylide proton.^{35,36} Very recently, allenyllithium was prepared by direct metallation of allene; condensation with benzophenone yielded the acetylenic alcohol exclusively whereas quenching with trimethylchlorosilane gave a mixture of allenic and acetylenic derivatives.³⁷ Dilithiopropyne has been prepared from both propyne and allene and formed only 1,3-bistrimethylsilylpropyne when quenched with trimethylchlorosilane;³⁷ it would be very interesting to attempt selective monoalkylation of dilithiopropyne, for such a transformation would make it a novel and useful propargylating reagent.



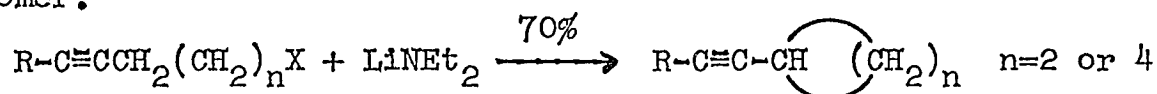
(34) P. M. Greaves, S. R. Landor, and D. R. J. Laws, Chem. Commun., 321 (1965).

(35) Treatment of a propargylic bromide with sodium or lithium failed to give a stable organometallic compound; J. H. Ford, C. D. Thompson, and C. S. Marvel, J. Amer. Chem. Soc., 57, 2619 (1935).

(36) Isomerization of propargylmagnesium complexes to propynylmagnesium compounds does occur on heating or standing for long periods of time: see references 15a and 15c.

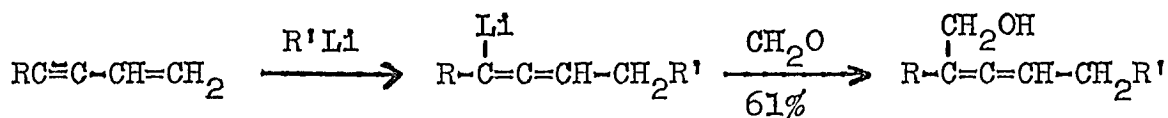
(37) F. Jaffe, J. Organometal. Chem., 23, 53 (1970).

Another route to propargyllithium reagents is direct metallation of internal acetylenes. A number of such studies have been carried out, but the preparation of polyolithiated and polysilylated compounds has been the object of this work.³⁸ A few examples of intramolecular alkylation have been reported, but the system was sterically constrained to give a single isomer.³⁹



Metal-halogen exchange between butyllithium and 1,1-diphenyl-3,3-dibromoallene has also been recently used to prepare allenyllithium compounds.⁴⁰

Finally, the addition of alkylolithium compounds to vinylacetylenes has been extensively explored by Russian workers, who reported substantial if not exclusive formation of allenic products upon treatment of the intermediate lithium complexes with a variety of reagents, such as water, carbonyl compounds, epoxides, carbon dioxide, oxygen, and iodine.⁴¹



(38) (a) J. E. Mulvaney, T. L. Folk, and D. J. Newton, J. Org. Chem., **32**, 1674 (1967); (b) R. West and G. A. Gornowicz, J. Amer. Chem. Soc., **93**, 1720 (1971); (c) J. Klein and S. Brenner, Ibid., **91**, 3094 (1969); (d) idem, J. Organometal. Chem., **18**, 291 (1969); (e) idem, Tetrahedron, **26**, 2345 (1970); (f) idem, J. Org. Chem., **36**, 1319 (1971); (g) J. Klein and E. Gurfinkel, Ibid., **34**, 3952 (1969).

(39) J. K. Crandall and D. J. Keyton, Chem. Commun., 1069 (1968).

(40) G. Köbrich and E. Wagner, Angew. Chem. Int. Eng. Ed., **9**, 524 (1970).

It is apparent from this survey that no reactive, regiospecific propargylating reagent is known and that much of the chemistry of propargylic organometallic compounds is still unexplored. In the remainder of this chapter, propargyl-lithium complexes prepared by metallation of 2-butyne and 1-trimethylsilylpropyne are examined and the use of lithio-1-trimethylsilylpropyne as a regiospecific propargylating reagent is discussed.⁴²

B. Alkylation of 2-Butynyllithium.

Although 2-butyne is not metallated by n-butyllithium in hexane at room temperature,⁴³ metallation is complete within five minutes in hexane or ether if one equivalent of TMED is added. This extraordinary increase in rate is attributed to coordination of the lithium cation by the tertiary amine, thereby dissociating the polymeric aggregates in which alkyl-lithiums exist in non-polar solvents and producing relatively unsolvated, highly reactive carbanions.⁴⁴ Treatment of the

(41) V. A. Kormer, et. al., J. Gen. Chem. USSR, 30, 231 (1960); 35, 571, 618, 963 (1965); idem, J. Org. Chem. USSR, 1, 1730, 1843 (1965); 2, 1719, 1897 (1966).

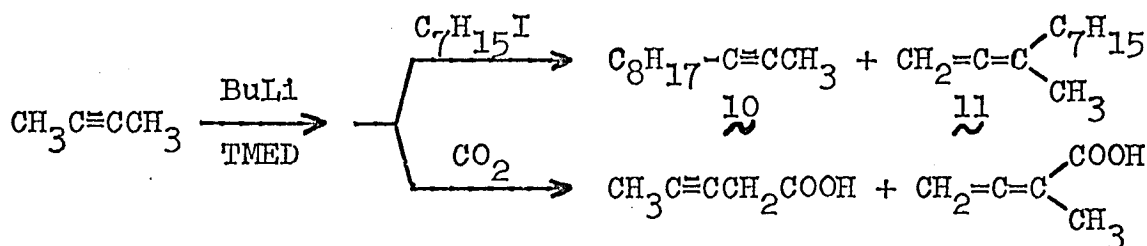
(42) Some of the work in this chapter has been published:
(a) E. J. Corey and H. A. Kirst, Tetrahedron Lett., 5041 (1968);
(b) E. J. Corey, H. A. Kirst, and J. A. Katzenellenbogen, J. Amer. Chem. Soc., 92, 6314 (1970).

(43) K. C. Eberly and H. E. Adams, J. Organometal. Chem., 3, 165 (1965).

(44) G. G. Eberhardt and W. A. Butte, J. Org. Chem., 29, 2928 (1964); A. W. Langer, Jr., Trans. N. Y. Acad. Sci., Ser. 2, 27, 741 (1965); C. G. Screttas and J. F. Eastham, J. Amer. Chem. Soc., 87, 3276 (1965).

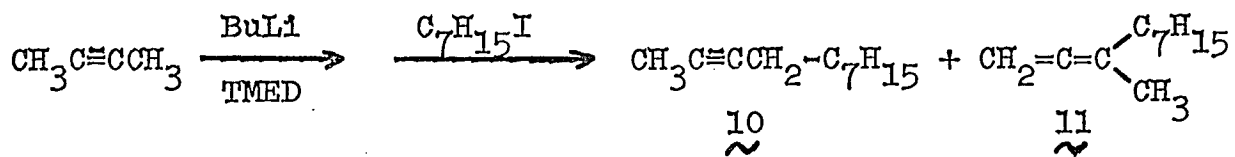
2-butyryllithium-TMED complex with 1-iodoheptane under a variety of reaction conditions (see table I) invariably yielded a mixture of 2-undecyne and 3-methyl-1,2-decadiene. Different solvents increased the proportion of undecyne in the order THF < DME < hexane < ether, while the proportion of methyldecadiene rose substantially when 1-bromoheptane was used instead of iodoheptane. Regioselectivity was favored with decreasing temperature, but problems simultaneously arose from metal-halogen exchange and slower reaction rates. Alkylation was considerably diminished in the presence of cuprous chloride, which also did not affect the isomer ratio (10/11).

Carboxylation of 2-butyryllithium likewise yielded a mixture of acetylenic and allenic acids.⁴⁵



(45) A mixture of allenic and acetylenic silanes has also been obtained from metallation and trimethylsilylation of 1-phenylpropyne: J. Klein and S. Brenner, Tetrahedron, 26, 2345 (1970); compare, however, with the reported formation of only the acetylenic silane: G. I. Pis'mennaya, L. M. Zubritskii, and K. V. Bal'yan, J. Org. Chem. USSR, 7, 244 (1971).

TABLE I. Alkylation of 2-Butynyllithium



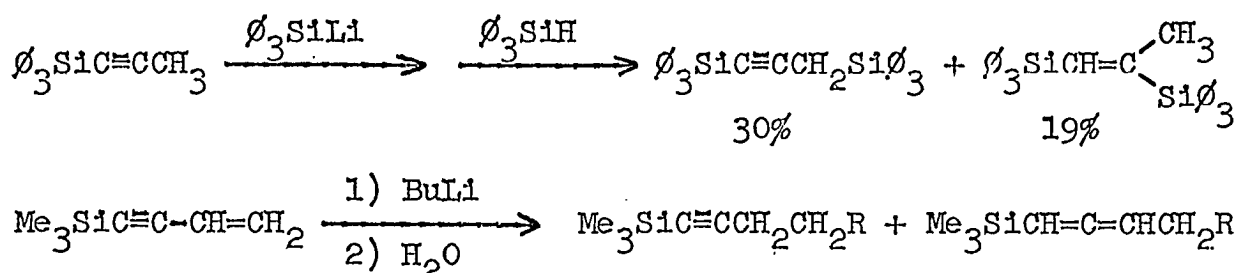
Solvent	Temp.	Time of Metallation	Time of Alkylation	Ratio of <u>10/11</u> (a)
Hexane	20°	5 min	16 hr	1.0
"	60°	" "	" "	1.1
Ether	35°	" "	45 min	1.2
"	0°	1 hr	18 hr	1.5 ^b
"	-30°	2.5 hr	1 hr	2.3 ^{c,d}
"	-20°	2 hr	16 hr ^e	1.9
"	-5° -78°	15 min 3.5 hr	6 hr (-78°)	1.7 ^d
THF	20°	5 min	45 min	0.56
"	-25°	1 hr	2 hr (-25°) 16 hr (r.t.)	0.30 ^c
DME	-5°	15 min	16 hr	0.79

^a Ratio determined by glpc analysis. ^b Ratio was 0.4 if 1-bromoheptane was used instead of iodoheptane. ^c *n*-Undecane was also present. ^d *n*-Tetradecane was also present. ^e Iodoheptane was added over 2.5 hr. period.

C. Utilization of Lithio-1-trimethylsilylpropyne.

1. Preparation and Alkylation.

In an attempt to sterically hinder the formation of allenes, the metallation and alkylation of 1-trimethylsilylpropyne was investigated. Previously, Gilman and Aoki had obtained 1,3-bis(triphenylsilyl)propyne without allenic by-products by treating lithio-1-triphenylsilylpropyne with either triphenylchlorosilane or triphenylsilane.⁴⁶ It was also known that approximately 1:1 mixtures of acetylenes and allenes were obtained on protonation of lithio-1-trimethylsilyl-3-alkylpropynes.⁴⁷



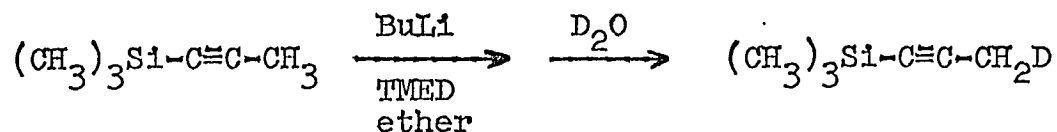
1-Trimethylsilylpropyne was easily prepared by silylation of propynyllithium and was readily metallated by the *n*-butyllithium-TMED complex (see table II).⁴⁸ Protonation of lithio-1-trimethylsilylpropyne (12) regenerated starting material whose infrared spectrum showed only a trace of allenic product.

(46) H. Gilman and D. Aoki, *J. Organometal. Chem.*, **2**, 44 (1964).

(47) A. A. Petrov, V. A. Kormer, and M. D. Stadnichuk, *J. Gen. Chem. USSR*, **30**, 2226 (1960); **31**, 1049 (1961).

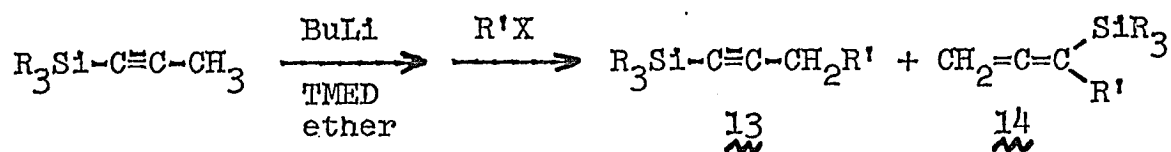
(48) The advantages of TMED were again demonstrated since *n*-butyllithium in refluxing hexane required 24 hours to completely metallate 1-trimethylsilylpropyne, conditions sufficiently severe to cause partial dilithiation: R. West and P. C. Jones, *J. Amer. Chem. Soc.*, **91**, 6156 (1969).

TABLE II. Rate of Generation and Stability of
Lithio-1-trimethylsilylpropyne



Time	-20°		-10°	
	Recovery ^a	Deuteration ^b	Recovery ^a	Deuteration ^b
1 hr	98%	80%	90%	85%
2 hr	95%	83%	90%	87%
3 hr	96%	84%	93%	87%
4 hr	97%	85%	90%	87%
5 hr	94%	84%	89%	87%
6 hr	92%	85%	89%	86%
7 hr	91%	84%		

^a Determined by glpc analysis. ^b Determined by nmr analysis.

TABLE III. Alkylation of Lithio-1-trialkylsilylpropyne^a

R	R'X	Glpc Analysis		Distilled	
		Yield of 13	Yield of 14	Yield of 13	Purity of 13
a. CH ₃	1-Iodohexane	90%	2%	77%	94%
b. "	Iodocyclohexane	-	3%	62%	90%
c. "	Benzyl bromide	79%	4%	74%	95%
d. "	Benzyl iodide	50%	3%	33%	91%
e. "	Geranyl bromide	82%	4%	65%	90% ^b
f. "	3,3-Dimethyl-allyl bromide	-	7%	78%	83% ^b
g. C ₂ H ₅	1-Iodohexane	98%	<0.5%	85%	92%
h. "	Benzyl bromide	75%	3%	71%	84%
i. "	Geranyl bromide	81%	6%	80%	83% ^b

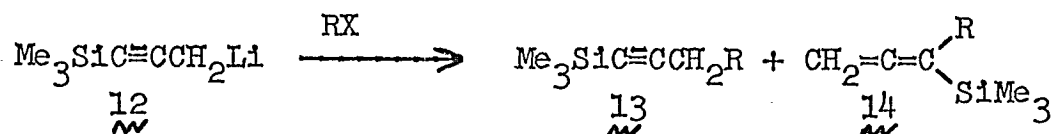
^a See p 21 for additional examples. ^b Several minor compounds were observed during glpc analysis.

TABLE IV. Effect of Solvent on Alkylation of Lithio-1-trimethylsilylpropyne

R	R'X	in ^a ether		in ^a THF	
		13 + 14	14	13 + 14	14
CH ₃	1-Iodohexane	2%	18%		
C ₂ H ₅	"	<0.5%	9%		
CH ₃	Geranyl bromide	4%	7%		
C ₂ H ₅	"	7%	6%		

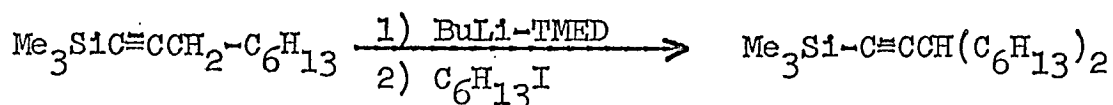
^a Ratios determined by glpc analysis

Treatment of lithio-1-trimethylsilylpropyne (12) in ethereal solution with a variety of alkyl halides produced the corresponding acetylenes (13) in good yield with less than 10% of the allenic isomers (14) simultaneously formed (glpc analysis) (see table III). The allenic products were



generally isolated by preparative glpc and identified by their infrared and nmr spectra; with geranyl bromide, γ -alkylation also occurred to a minor extent. The minor amount of allenic product was not eliminated by using lithio-1-triethylsilylpropyne except in the case of iodohexane. As previously found in alkylations of 2-butyneyllithium, the proportion of allenic product from iodohexane rose appreciably when THF was used as solvent; however, the ratio of products (13 and 14) formed from geranyl bromide was essentially identical in either THF or ether as solvent.

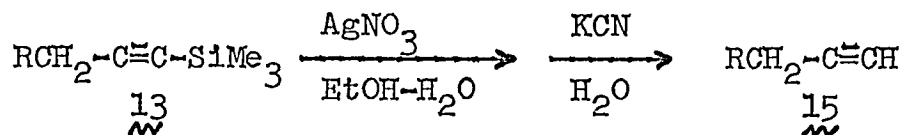
Following a procedure analogous to that for 1-trimethylsilylpropyne, 1-trimethylsilylnonyne was metallated and treated with 1-iodohexane, yielding 1-trimethylsilyl-3-hexyl-1-nonyne as the predominant product.⁴⁹ Consequently, non-linear acetylenes and carbonyl compounds derived from them can be readily obtained from lithio-1-trimethylsilylalkynes.



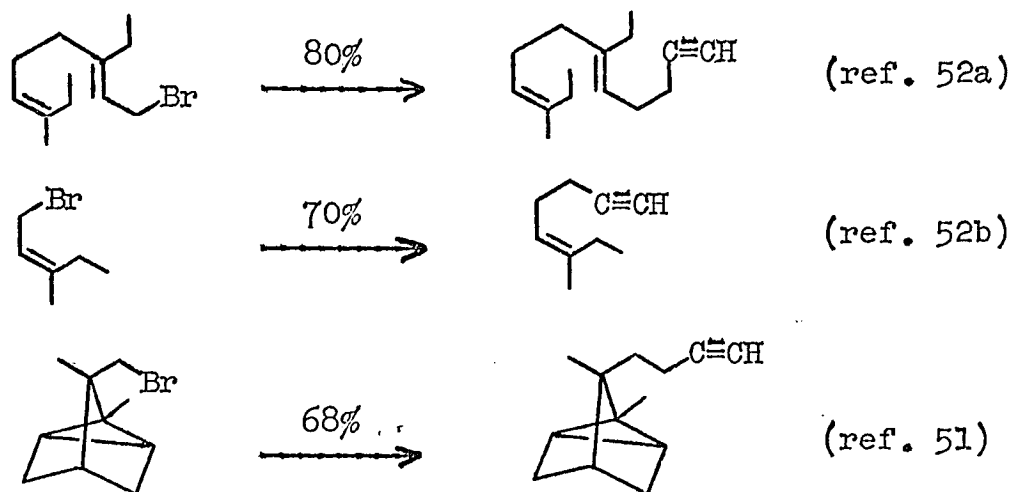
(49) A similar result has been reported from metallation of 1,3-bistriphenylsilylpropyne and alkylation with methyl iodide.⁴⁶

2. Conversion to Terminal Acetylenes.

The trimethylsilyl- and triethylsilylacetylenes were quantitatively converted to terminal acetylenes using silver nitrate in aqueous ethanol;⁵⁰ under these conditions, the allenic silanes (14) were recovered unchanged.



Lithio-1-trimethylsilylpropyne has already been employed in several isoprenoid syntheses;⁵¹⁻⁵³ its application in the synthesis of α -santalol will be discussed more fully in



(50) H. M. Schmidt and J. F. Arens, Rec. Trav. Chim. Pays-Bas, 86, 1138 (1967). For other methods of cleaving silylacetylenes, see H. Gilman, A. G. Brook, and L. S. Miller, J. Amer. Chem. Soc., 75, 4531 (1953); R. Eastmond and D. R. M. Walton, Chem. Commun., 204 (1968); C. S. Kraihanzel and J. E. Poist, ibid., 607 (1968); idem, J. Organometal. Chem., 8, 239 (1967).

(51) α -Santalol: E. J. Corey, H. A. Kirst, and J. A. Katzenellenbogen, J. Amer. Chem. Soc., 92, 6314 (1970).

(52) Cecropia juvenile hormone: (a) E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, ibid., 90, 5618 (1968); (b) E. J. Corey, J. A. Katzenellenbogen, S. A. Roman, and N. W. Gilman, Tetrahedron Lett., 1821 (1971).

chapter two. The utility of lithio-1-trimethylsilylpropyne appears limited, however, with highly reactive, base-sensitive halides, such as 1,4-dibromo-2-butene; in such cases, use of the milder propargylmagnesium bromide is necessary.⁵⁴

The sequence of alkylation by lithio-1-trimethylsilylpropyne and desilylation represents a novel propargylation procedure which gives higher yields and greater regioselectivity than is obtained with propargylmagnesium bromide. Alkylation of allylic halides presents an improved synthetic route to 1,5-enynes and unsymmetrical 1,5-dienes.⁵⁵ Furthermore, the terminal acetylenes (15) are precursors of acetylenic esters and carbinols and trisubstituted olefins derived from them (see pp 2-4). Finally, propargylation of saturated alkyl halides, which react poorly with Grignard reagents, can now be easily accomplished; even hindered halides, such as a neopentyl bromide, will react if a dipolar aprotic co-solvent such as HMPA is added.⁵¹

3. Rationalization of Regiospecificity Observed in Alkylations.

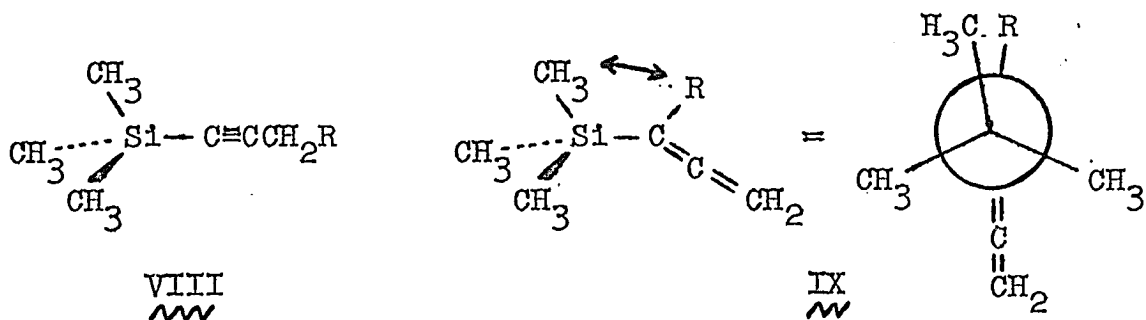
It seems likely that steric interactions play a major role in the regiospecific alkylation of lithio-1-trimethylsilylpropyne. No unfavorable steric repulsions exist in

(53) Sirenin: E. J. Corey and K. Achiwa, Tetrahedron Lett., 2245 (1970).

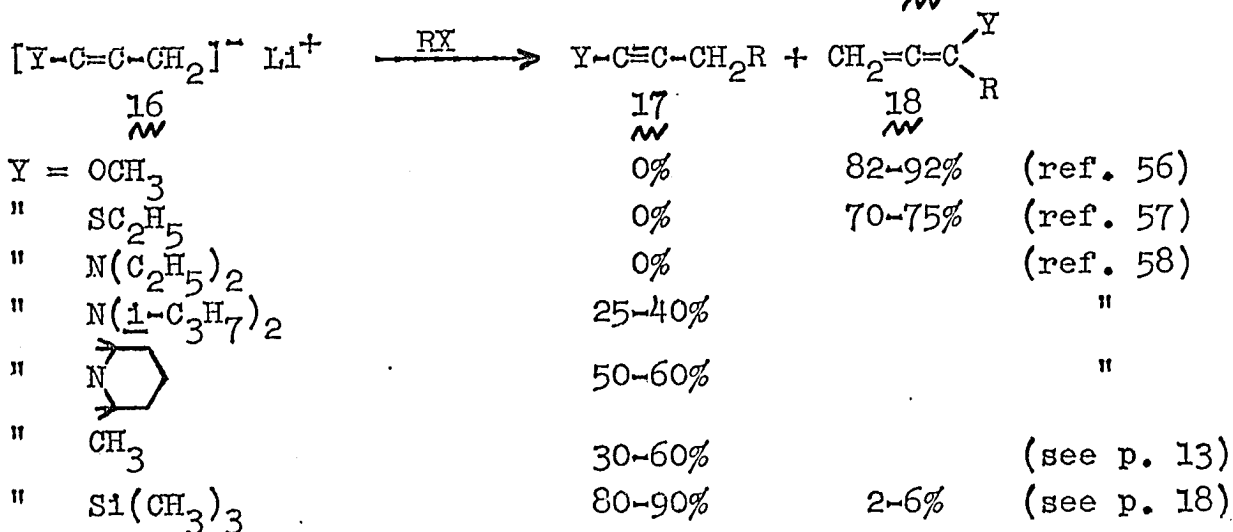
(54) R. E. Ireland, M. I. Dawson, and C. A. Lipinski, ibid., 2247 (1970).

(55) See chapter 3 for a discussion of 1,5-dienes.

the acetylenic silane (VIII) whereas an unfavorable, partially eclipsed conformation cannot be avoided in the allenic silane (IX). Consequently, formation of silylacetylene 13 is expected from steric considerations.



This hypothesis is supported by the results of alkylation of a number of lithio-1-substituted propynes (16); the



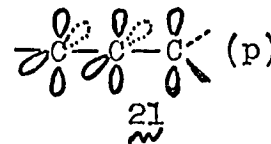
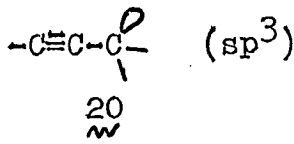
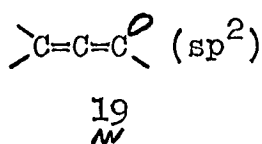
(56) S. Hoff, L. Brandsma, and J. F. Arens, Rec. Trav. Chim., **87**, 916 (1968); see also R. Mantione, et. al., ibid., **89**, 97 (1970); idem, C. R. Acad. Sci., Paris, Ser. C, **272**, 786 (1971); idem, Tetrahedron Lett., 591 (1971); idem, J. Organometal. Chem., **30**, 295 (1971).

(57) L. Brandsma, H. E. Wijers, and J. F. Arens, Rec. Trav. Chim. Pays-Bas, **82**, 1040 (1963). This reaction was performed in liquid ammonia whereas the others were carried out in ethereal solvents.

(58) D. E. Cane, Ph.D. Thesis, Harvard University, April, 1971, chapter 2; E. J. Corey and D. E. Cane, J. Org. Chem., **35**, 3405 (1970).

proportion of allenic product (18) markedly decreases as the substituent Y increases in size, as is particularly well-illustrated by the metallated ynamines (16, Y = NR₂).⁵⁸

Alkylation of 16 in the absence of steric hindrance might be expected to favor formation of allenic product (18) as a result of charge stabilization on the carbon atom adjacent to the heteroatom; in the absence of such stabilization, formation of neither product is particularly favored, as exemplified by alkylations with propargylmagnesium bromide (see pp 8-9). Furthermore, a higher electron density would be expected in an sp² orbital (19) compared to an sp³ orbital (20) (s-orbital effect),⁵⁹ although a fully delocalized anion (21) can also be written in which the charge resides only in p orbitals.⁶⁰



Of course, other effects such as coordination by the cation or solvent may also influence the regioselectivity of the reaction.

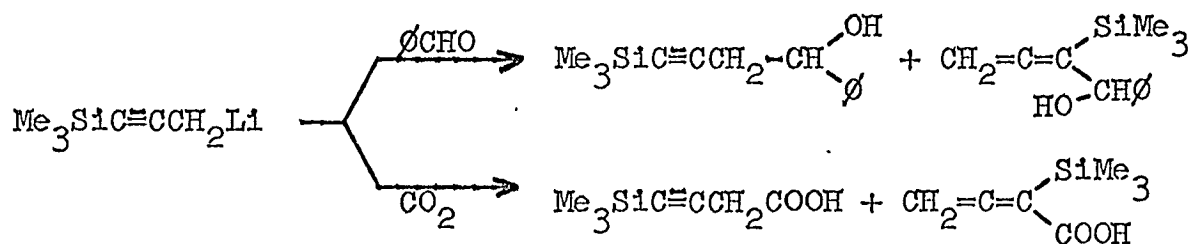
4. Condensation with Carbonyl Compounds.

Even though propargylic carbinols are easily obtained from propargylmagnesium or propargylaluminum compounds,^{15,16}

(59) D. J. Cram, Survey Prog. Chem., 4, 51-53 (1968).

(60) Such extended conjugated systems have recently been shown to be favored particularly with multiply charged anions derived from acetylenes: J. Klein and S. Brenner, J. Amer. Chem. Soc., 91, 3094 (1969).

it was of interest to briefly examine the reactions of lithio-1-trimethylsilylpropyne with carbonyl compounds. Condensation of either lithio-1-trimethyl- or triethylsilylpropyne with benzaldehyde yielded a mixture of propargylic and allenic carbinols in a 2:1 ratio; this ratio did not change when the reaction temperature was lowered. On the other hand, only the propargylic carbinol was obtained when lithio-1-trimethylsilylpropyne was treated with the more hindered benzophenone.⁶¹ Carboxylation of lithio-1-trimethylsilylpropyne gave a similar 2:1 mixture of acetylenic and allenic carboxylic acids. These



preliminary observations indicate that acetylenic products are formed exclusively from ketones, but not from less-hindered aldehydes or carbon dioxide. This result is not unexpected, for regioselectivity in both alkylation of halides and addition to carbonyl compounds is often not observed, due, most likely, to different reaction mechanisms.⁶²

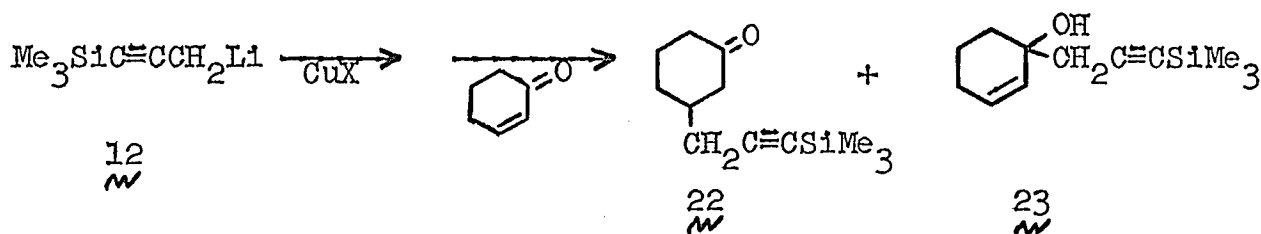
(61) The propargylic carbinol was also exclusively formed from 2-cyclohexenone: see p 25.

(62) See survey at the beginning of this chapter, ref. 53, 56, and 57, and compare reference 54 with A. Schaap, L. Brandsma, and J. F. Arens, Rec. Trav. Chim. Pays-Bas, **84**, 1200 (1965); idem, ibid., **86**, 393 (1967).

5. Conjugate Addition to α, β -Unsaturated Ketones.

1,4-Addition of propargylic Grignard reagents to α, β -unsaturated ketones does not occur,²⁰ although the effect of cuprous salts on this reaction has not been reported.⁶³ Furthermore, no propargylcopper complex has yet been prepared. It was of interest, therefore, to treat lithio-1-trimethylsilylpropyne with cuprous salts and attempt conjugate addition to an unsaturated ketone.⁶⁴

Lithio-1-trimethylsilylpropyne was treated with cuprous salts under a wide variety of conditions before addition of 2-cyclohexenone (see table V), but in all cases, the yield of the 1,4-adduct (22) was low; the predominant product was the 1,2-adduct (23), which was exclusively formed in the absence of copper salts. Unexpectedly, soluble lithium dialkylcuprate



complexes or soluble phosphine or phosphite-alkylcopper complexes were not formed in this system, in contrast to

(63) Propargylmagnesium bromide in the presence of cuprous salts has recently been found to yield mixtures of 1,2 and 1,4-addition products from cyclohexenone: unpublished results in these laboratories by H. H. Lee.

(64) The 1,4-adduct from cyclohexenone would be a useful precursor of bicyclo[3.2.1]octanes: G. Stork, S. Malhotra, H. Thompson, and M. Uchibayashi, *J. Amer. Chem. Soc.*, 87, 1148 (1965); E. J. Corey, M. Narisada, T. Hiraoka, and R. A. Ellison, *ibid.*, 92, 396 (1970).

TABLE V. Conjugate Addition of
 1-Trimethylsilylpropargylcopper Complexes

Cuprous Salt	Cu/Li	Solvent	RLi + CuX ^a		RCu + Δ C=O ^b		Yield ^c of $\underset{w}{22}$
			Temp	Time (min)	Temp	Time (min)	
CuI	1.0	ether	-10°	30	22°	10	10%
"	"	"	"	"	"	60	8%
"	"	"	"	"	-5°	10	15%
"	"	"	"	"	-20°	"	25%
"	"	"	"	"	"	60	15%
"	"	"	"	"	-35°	10	21%
"	"	"	"	"	"	60	23%
"	"	"	"	"	-50°	10	8%
"	"	"	"	"	"	60	16%
"	"	"	"	"	-78°	10	6%
"	"	"	"	"	"	60	10%
"	"	"	-20°	15	-20°	10	29%
"	3.0	"	"	"	"	"	26%
"	10.0	"	"	"	"	"	29%
"	0.25	"	"	"	"	"	20%
"	0.5	"	"	"	"	"	28% (e)
"	"	"	"	60	"	"	23%
"	"	"	"	90	"	"	27%
"	"	"	"	120	"	"	31%
"	"	"	-50°	15	-50°	60	23%
"	"	"	"	60	"	"	25%
"	"	"	-78°	15	-78°	"	16%
"	"	"	"	60	"	"	6%
"	"	THF	-20°	15	-20°	10	18% (d, f)
"	"	"	"	60	"	"	17% (d)
"	"	"	"	120	"	"	14% (d)
"	"	"	-50°	15	-50°	60	6%
"	2.0	"	"	"	"	"	5%
CuCl	0.5	ether	-20°	15	-20°	10	3% (d)
"	"	"	"	90	"	"	1% (d)
CuI-PBu ₃	1.0	"	"	15	"	"	10%
"	"	"	"	90	"	"	14%
"	0.5	"	24°	15	24°	10	9%
CuI-P(OMe) ₃	1.0	"	-20°	15	-20°	10	2%
"	"	"	"	90	"	"	1%
"	0.5	"	24°	15	24°	10	0%

^a Time and temperature at which $\underset{w}{12}$ and CuX were stirred before addition of cyclohexenone. ^b Time and temperature at which reaction was stirred after addition of cyclohexenone. ^c Determined by glpc. ^d Homogeneous reaction. ^e Isolated yields of 20% of $\underset{w}{22}$ and 55% of $\underset{w}{23}$. ^f Isolated yields of 11% of $\underset{w}{22}$ and 63% of $\underset{w}{23}$.

previously reported examples.^{65,66} However, it is unlikely that the high proportion of 1,2-adduct (23) is due to incomplete conversion of alkylolithium to alkylcopper complexes, since the yield of 1,4-adduct (22) was not improved by a large excess of cuprous iodide, but was diminished by using less than that needed to quantitatively form a lithium dialkylcuprate complex. Furthermore, the yield of 1,4-adduct was not increased in those few homogeneous reactions; in fact, the lower yield of conjugate addition in THF compared to that in ether is in accord with previous observations.^{65a}

It has been shown that conjugate addition occurs less readily with copper complexes derived from relatively stable ligands than with complexes from saturated alkyl groups.⁶⁷ It is also known that propargylic organometallic compounds add to carbonyl groups much more rapidly than do their saturated analogs.²⁰ Thus, the high percentage of 1,2- versus 1,4-addition from propargylcopper complexes is probably the combined result of increased reactivity toward carbonyl addition and decreased reactivity toward conjugate addition relative to their saturated analogs.

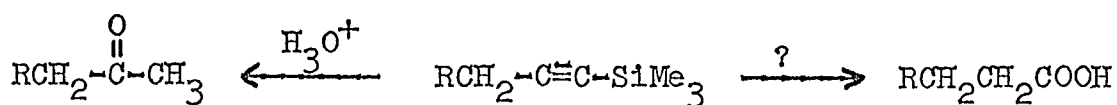
(65) (a) H. O. House, W. L. Respass, and G. M. Whitesides, J. Org. Chem., 31, 3128 (1966); (b) H. O. House and W. F. Fischer, Jr., ibid., 33, 949 (1968).

(66) Cuprous iodide-tris(diisopropyl sulfide) also formed an insoluble complex with 12 and produced a mixture of 22 and 23: E. J. Corey and H. H. Lee, unpublished results.

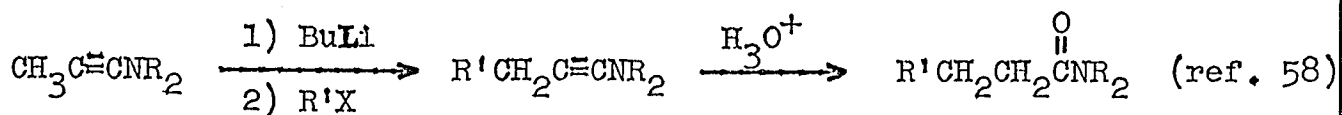
(67) H. O. House and W. F. Fischer, Jr., J. Org. Chem., 34, 3615 (1969).

6. Conversion to Carboxylic Acids.

Acid-catalyzed hydration of silylacetylenes proceeds in a Markovnikov manner to produce methyl ketones.⁶⁸ If an anti-Markovnikov hydration and oxidation could be achieved,⁶⁹ lithio-1-trimethylsilylpropyne could be utilized as a three-carbon nucleophile containing a masked terminal carboxyl group [-CH₂CH₂COOH]. The only example of such a three-carbon



chain extension employs the sequence of metallation, alkylation, and hydration of 1-dialkylaminopropyne, for which the overall yield is only 20-30%.⁵⁸ A somewhat more indirect route can be constructed via the corresponding aldehyde.^{71,72}



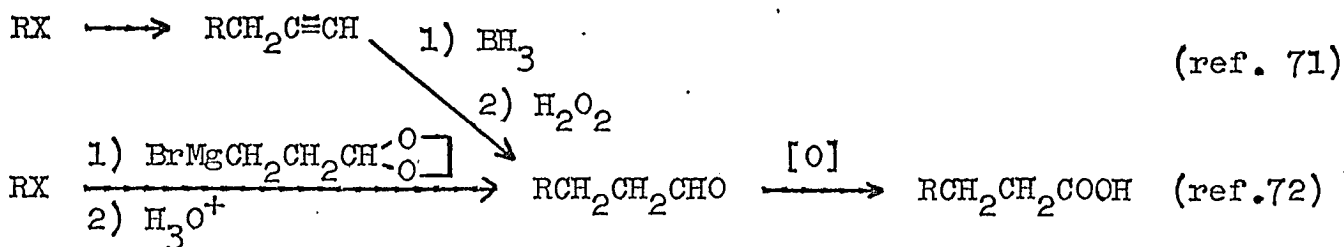
(68) A. D. Petrov and L. L. Shchukovskaya, J. Gen. Chem. USSR, 25, 1083 (1955).

(69) Anti-Markovnikov hydration of silylacetylenes produces α -silylketones which are quickly cleaved to aldehydes in strongly basic solution.⁷⁰ Free aldehydes are unlikely to be intermediates in the present case since they are prepared from terminal acetylenes under these conditions.⁷¹

(70) A. G. Brook, Advan. Organometal. Chem., 7, 95 (1968).

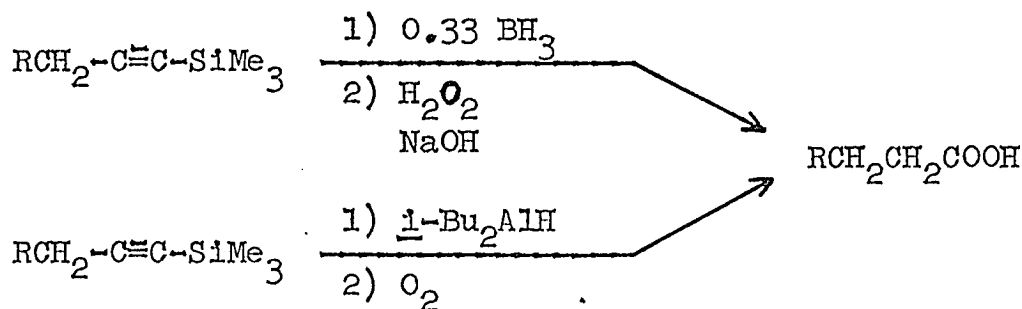
(71) H. C. Brown and G. Zweifel, J. Amer. Chem. Soc., 81, 1512 (1959); 83, 3834 (1961).

(72) G. Büchi and H. Wüest, J. Org. Chem., 34, 1122 (1969).



Hydroboration and alkaline peroxide oxidation successfully converted 1-trimethylsilylnonyne into nonanoic acid; the 43% conversion can undoubtedly be increased since a substantial amount of starting material was recovered. However, use of one mole of borane per mole of acetylene led to a lower yield of acid and formation of saturated silanes.

Hydroalumination and oxidation by oxygen of 1-trimethylsilylnonyne was also briefly examined since the direction of hydroalumination has been determined;⁷³ in this case, a 37% conversion to nonanoic acid was achieved. These preliminary experiments demonstrate a novel three-carbon, terminal-carboxylic-acid synthon which should prove useful in synthesis.



(73) J. J. Eisch and M. W. Foxton, J. Organometal. Chem., 11, P24 (1968).

D. Experimental Section.

1. Experimental Details. The details described below concerning materials, procedures, and instrumentation apply to all experimental sections of this thesis.

a. General Procedures.

All reactions involving air- or moisture-sensitive compounds were conducted under an atmosphere of argon introduced by alternately evacuating and filling the reaction vessel with argon several times; solvents for such reactions were flushed with argon in an analogous manner. During the reaction, the system was open to an argon-filled balloon through a three-way stopcock. Liquids were introduced or removed from the reactions by syringe through a rubber serum cap wired to a side-arm of the reaction vessel. Transfers from reactions at low temperatures were made by a pre-cooled syringe moistened with solvent at the reaction temperature. Solid reagents were added to reactions via a funnel through a neck of the vessel from which a stream of argon flowed.

All reactions were stirred magnetically unless otherwise noted. Solvent mixtures are expressed in parts by volume. Organic solutions of reaction mixtures were dried by extracting with saturated sodium chloride solution and standing over anhydrous magnesium sulfate unless otherwise noted; removal of solvent was effected at room temperature using a Büchi rotary evaporator at aspirator pressure unless otherwise stated.

b. Reagents and Solvents.

All reactions involving nickel carbonyl (volatile and toxic!) were conducted in a well-ventilated hood. Nickel carbonyl was poured into a small flask from a lecture bottle (Matheson) as needed and added to the reaction via syringe whose needle extended below the surface of the solvent; excess nickel carbonyl was decomposed in concentrated nitric acid. Diisobutylaluminum hydride (pyrophoric!) was transferred under argon from a lecture bottle (Alfa Inorganics) into a dry flask and used neat. Solutions of lithium aluminum hydride in THF or ether were prepared by stirring the solid reagent in solvent overnight and filtering through Celite and glass wool in a thoroughly dry Schlenk tube under positive argon pressure. The concentration of solutions of LiAlH_4 and diborane were determined by measuring the hydrogen evolved from an aliquot quenched in dilute acid. Sodium hydride was washed free of mineral oil by trituration with pentane three times. The concentration of commercial alkyl-lithium reagents (Foote Mineral Co.) was determined by titration with 2-butanol in xylene using 1,10-phenanthroline as indicator.⁷⁴

Paraformaldehyde was dried for several days in vacuo over phosphorus pentoxide, and lithium bromide was dried in vacuo at 110° . Anhydrous p-toluenesulfonic acid was prepared

(74) S. C. Watson and J. F. Eastham, J. Organometal. Chem., 9, 165 (1967).

by azeotropic distillation of water with toluene. Geranyl bromide was prepared from geraniol and phosphorus tribromide in ether at 0° for 12-15 hours.⁷⁵

Common solvents of reagent grade were used without purification. DMF, DMSO, HMPA, and N-methylpyrrolidone were distilled from calcium hydride under reduced pressure. THF (in a recycling still), DME, diglyme, and tetraglyme were distilled from LiAlH₄ under argon, the latter two under reduced pressure.

Trimethylchlorosilane, ethyl acetate, and methanesulfonyl chloride were distilled from phosphorus pentoxide, 2,3-dihydropyran and 2,5-dihydrofuran were distilled from sodium, and TMED, triethylamine, thioanisole, and dimethyl methylphosphonate were distilled from calcium hydride, the latter two under reduced pressure. 2-Butyne, 2-butenone, methyl crotonate, mesityl oxide, trimethyl phosphite, methallyl alcohol, *t*-butyl mercaptan, 2-decynol, 2-cyclohexenone, and allyl iodide (in subdued light) were distilled before use, the latter three under reduced pressure. Pyridine-sulfur trioxide complex (Aldrich Chemical Co.), propynyllithium (Foote Mineral Co.), triethylchlorosilane (Peninsular Chemresearch), cuprous iodide (Fisher purified grade), and silver tetrafluoroborate (Alfa Inorganics) were used without further purification.

(75) J. M. Osbond, J. Chem. Soc., 5270 (1961).

c. Instrumentation.

Infrared spectra were recorded for carbon tetrachloride solutions with a Perkin-Elmer Model 137 spectrometer, calibrated with the 1601 cm^{-1} absorption of polystyrene. Nuclear magnetic resonance (nmr) spectra were determined using deuteriochloroform as solvent with Varian A-60 and T-60 spectrometers, and data are reported as δ in parts per million downfield from tetramethylsilane (internal standard, $\delta = 0$). Optical rotations were measured using chloroform as solvent with a Perkin-Elmer Model 141 polarimeter. Mass spectra and exact mass measurements were determined using an AEI Model MS-9 double focusing spectrometer at 70 eV. Melting points were determined with a Büchi melting point apparatus and are corrected; boiling points are uncorrected. F & M Model 810, 5750, and 609 gas chromatographs (nitrogen carrier gas, 30 ml/min, flame ionization detector) were used for analytical gas-liquid phase chromatography (glpc), and F & M Model 300 and Varian Aerograph Model A-700 chromatographs (helium carrier gas, 60-100 ml/min, thermal conductivity detector) were used for preparative glpc. Product ratios and yields were calculated from peak area ratios, corrected for differences in detector response if an internal standard was used; retention times are abbreviated as t_r and were calculated from the time of injection. The glpc columns used are listed in Table VI.

TABLE VI. Gas Chromatography Columns.

Column	Length (ft)	Diameter (in)	Liquid Phase	Solid Support
A	3	0.125	5% Carbowax 20M + 2% KOH	Chromosorb W ^a
B	10	0.125	10% Carbowax 20M	Chromosorb W
C	15	0.125	10% Carbowax 20M	Diatoport S
D	16	0.125	5% Carbowax 20M + 2% KOH	Chromosorb W
E	10	0.125	5% DEGS	Chromosorb W
F	10	0.125	10% DEGS	Chromosorb W
G	15	0.125	10% LAC-728	Diatoport S
H	16	0.125	10% LAC-728	Diatoport S
I	3	0.125	5% SE-30	Gaschrom Q
J	10	0.125	5% SE-30	Gaschrom Q
K	20	0.125	10% SE-30	Diatoport S Hi-Pak
L	2.5	0.125	3% OV-7	Gaschrom Q
M	10	0.125	3% OV-17	Gaschrom Q
N	8	0.25	20% LAC-446	Chromosorb W
O	10	0.25	5% LAC-728	Diatoport S
P	10	0.25	5% Carbowax 20M + 2% KOH	Diatoport S
Q	6	0.25	2% SE-30	Diatoport S
R	10	0.25	5% SE-30	Diatoport S
S	12	0.375	16% LAC-446	Diatoport S
T	10	0.375	10% FS1-1265	Diatoport S
U	10	0.375	20% SE-30	Chromosorb W

^a Acid-washed, dimethylchlorosilanized.

d. Thin Layer Chromatography.

Analytical thin layer chromatography (tlc) was carried out using Merck precoated, glass-backed silica gel F-254 plates (0.25 mm), developed once unless otherwise stated. Visualization agents used are designated as follows: A - ultraviolet illumination; B - 5% phosphomolybdic acid in ethanol; C - 2% vanillin in 1:1 85% phosphoric acid and ethanol; D - 3% cupric acetate in 1:5 85% phosphoric acid and water; E - 0.5% 2,4-dinitrophenylhydrazine in 2N hydrochloric acid; and F - 2% ceric sulfate in 2N sulfuric acid; G - iodine vapor; sprayed plates were heated to 150°.

Preparative tlc was carried out with 20-cm square glass plates coated with Merck silica gel PF-254 (2 mm); commercially available precoated plates (0.5 and 2 mm) were occasionally used. Products were visualized by ultraviolet illumination, observing the raised forward edge of a band, or spraying an edge of the plate with a visualization agent and heating the edge. Buffered plates were prepared using sodium phosphate buffer solution instead of water.

e. Microanalyses.

Microanalyses were performed by Scandinavian Micro-analytical Laboratories, Herlev, Denmark; Schwarzkopf Micro-analytical Laboratory, Woodside, N. Y.; and Alfred Bernhardt Microanalytical Laboratory, Mulheim, Germany.

2. 2-Butynyllithium.

Carboxylation of 2-Butynyllithium. a. In THF.

n-Butyllithium (16.0 ml of 1.6 M in hexane, 25.5 mmol) in THF (40 ml) at -70° was treated with TMED (3.94 ml, 25.5 mmol) and 2-butyne (2.0 ml, 25.5 mmol); aliquots were quenched with powdered carbon dioxide, warmed to room temperature, acidified, and extracted with ether. After 6 hr, only valeric acid was formed (nmr analysis), so the reaction was warmed to -50° for 20 min, yielding a mixture of valeric and unsaturated acids. After 20 min at -20° , valeric acid was no longer formed and an approximate 1:2 mixture of 3-pentynoic acid and 2-methyl-2,3-butadienoic acid was obtained: ir 3510-2620 (very broad, COOH), 2242 (w, C \equiv C), 1965 and 1938 (w, C=C=C), 1755 (sh) and 1706 cm^{-1} (s, C=O); nmr δ 1.88 (m, CH₃), 3.32 (q, J = 3 Hz, CH₂-COOH), 5.17 (q, J = 3 Hz, CH₂=C=C), 11.10 (s, COOH).

b. In Hexane. The reaction was repeated in hexane (25 ml) for 5 min at room temperature, also yielding a 1:2 mixture of 3-pentynoic acid and 2-methyl-2,3-butadienoic acid.

General Procedure for Alkylation of 2-Butynyllithium.

One equivalent each of n-butyllithium in hexane, TMED, and 2-butyne were successively added to solvent (5 ml per ml of BuLi solution) at the desired temperature, and the mixture was stirred for the stated period of time (see table I, p 15); the reactions were deep yellow except those in ether. Upon addition of 1-iodoheptane, a white precipitate slowly formed.

After the given period of time, the reaction was diluted with ether, extracted with dilute hydrochloric acid, dried, and analyzed by glpc (column G, 110° or N, 150°); the results are tabulated in table I.

3-Methyl-1,2-decadiene. From the reaction in THF at -25° (see table I), a sample of 3-methyl-1,2-decadiene was isolated by preparative glpc (column T, 150°): ir 1953 cm⁻¹ (m, C=C=C); nmr δ 0.90 (t, 3, CH₃), 1.27 (broad s, 10, n-C₅H₁₀), 1.66 (t, 3, J = 3 Hz, CH₃-C=C), 1.88 (broad s, 2, CH₂-C=C), 4.53 (q, 2, J = 3 Hz, CH₂=C); glpc t_r 3.4 min (column G, 110°).

2-Undecyne. An authentic sample of 2-undecyne was prepared by alkylation of propynylsodium (from propyne and sodium methylsulfinylmethide⁷⁶) with 1-iodooctane in DMSO: ir 2050 cm⁻¹ (vs, C≡C); nmr δ 0.89 (t, 3, CH₃), 1.28 (broad d, 12, n-C₆H₁₂), 1.78 (t, 3, J = 2.5 Hz, CH₃-C≡C), 2.11 (broad, 2, CH₂-C≡C); glpc t_r 6.4 min (column G, 110°).

Alkylation in the Presence of Cuprous Chloride. 2-Butynyllithium was prepared in ether at -5° for 30 min as described above and cooled to -78°. The mixture was treated with cuprous chloride (0.5 equiv) at -78° for 2 hr and then with 1-iodoheptane (1 equiv) at -78° for 6 hr before warming to 0° overnight. The product was isolated and analyzed as described above; the ratio of 10/11 was 1.4 using 0.5 equivalent cuprous chloride and 1.6 using 0.05 equivalent cuprous

(76) E. J. Corey and M. Chaykovsky, J. Amer. Chem. Soc., 84, 866 (1962); ibid., 87, 1345 (1965).

chloride compared with 1.7 in the absence of cuprous chloride. The amount of recovered iodoheptane increased substantially with increasing amounts of cuprous chloride.

If cuprous chloride was added at -45° instead of -78° , neither 10 or 11 were formed and iodoheptane was recovered.

3. Lithio-1-trialkylsilylpropynes.

a. Preparation.

1-Trimethylsilylpropyne. Trimethylchlorosilane (56 ml, 0.44 mmol) was added to a suspension of propynyllithium (21.2 g, 0.46 mmol) in anhydrous diglyme (250 ml) at 0° with vigorous (Hershberg) stirring, and the mixture was stirred at 0° for 10 hr, filtered, and slowly distilled through a 30-cm Vigreux column to yield 43.7 g (89%) of 1-trimethylsilylpropyne: bp $97-100^{\circ}$ [lit.⁷⁷ bp $99-100^{\circ}$]; ir 2188 (s, $C\equiv C$), 1248 (s, Me_3Si), 1028 (s), 845 cm^{-1} (vs, Me_3Si); nmr δ 0.13 (s, 9, Me_3Si), 1.87 (s, 3, $CH_3-C\equiv C$); glpc t_r 2.8 min (column H, 80°).

1-Triethylsilylpropyne. A vigorously stirred suspension of propynyllithium (3.44 g, 74.5 mmol) was treated with triethylchlorosilane (10.0 ml, 59.6 mmol) in refluxing ether (40 ml) for 48 hr. The ethereal mixture was cooled, carefully treated with water, separated from the aqueous layer, dried, and concentrated under reduced pressure. The residual liquid was distilled to yield 7.48 g (81%) of 1-triethylsilylpropyne: bp $59-63^{\circ}$ (17 mm) [lit.⁷⁷ bp $169.5-170.5^{\circ}$]; ir 2203 (s, $C\equiv C$),

(77) A. D. Petrov, L. L. Shchukovskaya, and Y. P. Egorov, Dokl. Akad. Nauk SSSR, 93, 293 (1953); Chem. Abstr., 48, 13616 (1954).

1018 (vs), 717 cm^{-1} (vs); nmr δ 0.49, 0.51, 0.63, 0.71, 0.73 (m, 6, $\text{CH}_2\text{-Si}$), 0.87-1.17 with two strong peaks at 0.87 and 0.99 (m, 9, CH_3), 1.90 (s, 3, $\text{CH}_3\text{-C}\equiv\text{C}$); glpc t_r 3.8 min (column H, 120°).

Rate of Metallation and Recovery of 1-Trimethylsilylpropyne. 1-Trimethylsilylpropyne (1.35 g, 12.0 mmol), TMED (1.84 ml, 12.0 mmol), methylcyclohexane (1.00 ml, internal glpc standard), and n-butyllithium in pentane (7.5 ml of 1.6 M, 12.0 mmol) were successively added to ether (40 ml) with stirring at -10 or -20° . Aliquots periodically withdrawn were quenched with D_2O , extracted with dilute hydrochloric acid, dried, and analyzed by glpc (column D, 80°) for recovered 1-trimethylsilylpropyne (see table II, p 17). The aliquots were then concentrated through a short Vigreux column at atmospheric pressure and analyzed by nmr for the extent of deuteration (see table II). The infrared spectrum of deuterated product showed only a trace of allenic absorption.

b. Alkylation (See Table III, p 18).

1-Trimethylsilylnonyne. i. In Ether. n-Butyllithium in pentane (20 ml of 1.19 M, 23.8 mmol) was freed of solvent in vacuo, and the residue was cooled to -10° . Anhydrous ether (40 ml), TMED (3.65 ml, 23.8 mmol), and 1-trimethylsilylpropyne (3.67 ml, 23.8 mmol) were successively added, and the solution was stirred between -10 and -15° for 4 hr, forming a precipitate in 1-2 hr which redissolved if the temperature rose above -10° . The mixture was treated with 1-iodohexane

(3.0 ml, 19.0 mmol, 0.8 equiv) at -10° for 1 hr and at 0° for 16 hr and then quenched, extracted twice with dilute hydrochloric acid, and dried. n-Tetradecane (glpc standard) was added to a measured aliquot of the known total volume of ether solution for glpc analysis; product yields and retention times were: 13a, 90%, 5.3 min; 14a, 2%, 4.3 min; n-tetradecane, 6.6 min (column H, 120°). The crude product was distilled through a 30-cm Holtzmann column to give 2.83 g (77%) of 1-trimethylsilylnonyne: bp $100-101^{\circ}$ (16 mm) [lit.^{50a} bp $44-51^{\circ}$ (0.2-0.5 mm)]. A pure sample was isolated by preparative glpc (column P, 100°): ir 2183 (s, $C\equiv C$), 1248 (s, Me_3Si), 845 cm^{-1} (vs, Me_3Si); nmr δ 0.14 (s, 9, Me_3Si), 0.88 (t, 3, CH_3), 1.30 (broad d, 10, $n-C_5H_{10}$), 2.21 (t, 2, $CH_2-C\equiv C$); mass spectrum parent m/e 196.

Anal. Calcd for $C_{12}H_{24}Si$: C, 73.38; H, 12.32. Found: C, 73.63; H, 12.19.

Analogous reactions run on a 2-3 mmol scale showed that unreacted iodohexane was recovered if 0.9 equiv was used whereas iodohexane was completely consumed if only 0.8 equiv was added. Maximum yields of alkylated product were obtained with a minimum of solvent and metallation periods of at least 3 hr. Alkylation was almost maximal within 2 hr after addition of iodohexane (2 hr, 83%; 20 hr, 85%).

ii. In THF. The reaction was run as described in part i using the following amounts of reagents: n-butyllithium (2.15 ml of 1.19 M, 2.56 mmol), THF (5 ml), TMED (0.40 ml, 2.56 mmol), 1-trimethylsilylpropyne (0.40 ml, 2.56 mmol), and

1-iodohexane (0.34 ml, 2.18 mmol); metallation and alkylation periods of 3 hr and 20 hr respectively at -20° were used. A pure sample of 3-trimethylsilyl-1,2-nonadiene was isolated by preparative glpc (column S, 135°): ir 1927 (s, C=C=C), 1245 (s, Me₃Si), 840 cm^{-1} (vs, Me₃Si); nmr δ 0.09 (s, 9, Me₃Si), 0.90 (t, 3, CH₃), 1.31 (m, 8, n-C₄H₈), 1.86 (m, 2, CH₂-C=C), 4.35 (m, 2, CH₂=C).

1-Trimethylsilyl-3-cyclohexylpropyne. Lithio-1-trimethylsilylpropyne (23.8 mmol) in ether, prepared as described above, was treated with freshly distilled iodocyclohexane (2.46 ml, 19.0 mmol) for 1 hr at -15° and 6 hr at 0° . Distillation of the crude product yielded 2.27 g (62%) of 1-trimethylsilyl-3-cyclohexylpropyne: bp 47° (0.2 mm); ir 2190 (s, C \equiv C), 1256 (s, Me₃Si), 850 cm^{-1} (vs, Me₃Si); nmr δ 0.14 (s, 9, Me₃Si), 1.10-1.88 (very broad m, 11, ring protons), 2.07 and 2.16 (m, 2, CH₂-C \equiv C); mass spectrum parent m/e 194; glpc t_r 3.4 min (column E, 120°). An analytical sample was obtained by preparative glpc (column U, 200°).

Anal. Calcd for C₁₂H₂₂Si: C, 74.13; H, 11.41. Found: C, 74.34; H, 11.62.

trans-1-Trimethylsilyl-6,10-dimethylundeca-5,9-diene-1-yne. Lithio-1-trimethylsilylpropyne (25.0 mmol) in ether, prepared as described above, was treated with freshly prepared geranyl bromide (3.8 ml, 20.3 mmol) for 18 hr at 0° . Glpc analysis using tetrahydronaphthalene as internal standard (t_r 7.8 min) showed three components: 13e, 82%, 6.6 min; 14e, 4%, 5.6 min; and a third compound, 4%, 4.5 min (column H,

180°). Distillation of the crude product through a 30-cm Holtzmann column gave 3.24 g (65%) of the title compound: bp 84-86° (0.04 mm). A pure sample was isolated by preparative glpc (column P, 130°): ir 2179 (s, C≡C), 1665 (w, C=C), 1248 (s, Me₃Si), 845 cm⁻¹ (vs, Me₃Si); nmr (# 1) δ 0.14 (s, 9, Me₃Si), 1.62 (s, 6, cis-CH₃), 1.68 (s, 3, trans-CH₃), 2.02, 2.07, 2.20 and 2.24 (m, 8, allylic CH₂), 5.15 (m, 2, CH=C); mass spectrum parent m/e 248.

Anal. Calcd for C₁₆H₂₈Si: C, 77.34; H, 11.36. Found: C, 77.02; H, 11.31.

The two minor components were likewise isolated by preparative glpc. The compound with t_r 5.6 min was the isomeric allene, 3-trimethylsilyl-6,10-dimethyl-1,2,5,9-undecatetraene: ir 1949 (s, C=C=C), 1236 (s, Me₃Si), 836 cm⁻¹ (vs, Me₃Si); nmr δ 0.10 (s, 9, Me₃Si), 1.60 (s, 6, cis-CH₃), 1.67 (s, 3, trans-CH₃), 2.02-2.24 (m, 6, allylic CH₂), 4.35 (t, 2, J = 3 Hz, CH₂=C=C), 5.03 (m, 2, CH=C).

The compound with t_r 4.5 min was identified as 1-trimethylsilyl-4-vinyl-4,8-dimethyl-nona-7-ene-1-yne: ir 2198 (s, C≡C), 1241 (s, Me₃Si), 905 (s, C=CH₂), 837 cm⁻¹ (vs, Me₃Si); nmr δ 0.14 (s, 9, Me₃Si), 1.07 (s, 3, tertiary CH₃), 1.58 and 1.67 (s, 8, cis- and trans-CH₃ overlapping CH₂), 2.22 (s, 4, CH₂-C≡C overlapping CH₂-C=C), 4.90-5.20 with maxima at 5.09 and 5.12 (m, 4, vinyl).

1-Trimethylsilyl-4-phenyl-1-butyne. Lithio-1-trimethylsilylpropyne (25 mmol) in ether was treated with benzyl

bromide (2.52 ml, 21.3 mmol) for 18 hr at 0°. Glpc analysis using naphthalene as internal standard (t_r 8.9 min) showed two products: 13c, 79%, 5.2 min, and 14c, 4%, 4.1 min (column H, 200°). Distillation of the crude product through a 15-cm Holtzmann column gave 3.18 g (74%) of the title compound: bp 58-59° (0.05 mm). A pure sample was isolated by preparative glpc (column P, 140°): ir 2179 (s, C≡C), 1248 (s, Me₃Si); 845 (vs, Me₃Si), 696 cm⁻¹ (s, phenyl); nmr δ 0.13 (s, 9, Me₃Si), 2.33-2.99 with maxima at 2.48, 2.58, 2.73, and 2.83 (m, 4, CH₂-CH₂), 7.24 (s, 5, phenyl); mass spectrum parent m/e 202.

Anal. Calcd for C₁₃H₁₈Si: C, 77.15; H, 8.96. Found: C, 77.28; H, 9.09.

The minor component, 3-trimethylsilyl-4-phenyl-1,2-butadiene, was also isolated by preparative glpc: ir 1931 (s, C=C=C), 1245 (s, Me₃Si), 843 (vs, Me₃Si), 697 cm⁻¹ (s, phenyl); nmr δ 0.03 (s, 9, Me₃Si), 3.34 (t, 2, J = 2.7 Hz, CH₂-Ø), 4.33 (t, 2, J = 2.7 Hz, CH₂=C), 7.23 (s, 5, phenyl).

1-Trimethylsilyl-6-methylhepta-5-ene-1-yne. Lithio-1-trimethylsilylpropyne (42 mmol) was treated with 3,3-dimethylallyl bromide (5.00 g, 33.6 mmol) as described above. Distillation⁷⁸ of the crude product through an 8-cm Vigreux column yielded 4.68 g (78%) of the title compound: bp 74-77° (4 mm); ir 2198 (s, C≡C), 1241 (s, Me₃Si), 838 cm⁻¹ (vs,

(78) Distillation performed by Dr. S. A. Roman.

Me₃Si); nmr δ 0.11 (s, 9, Me₃Si), 1.63 (s, 3, cis-CH₃), 1.71 (s, 3, trans-CH₃), 2.15-2.20 (m, 4, allylic CH₂), 5.15 (m, 1, vinyl); mass spectrum parent m/e 180; glpc t_r 5.5 min (column H, 120°). An analytical sample was obtained by preparative glpc (column U, 180°).

Anal. Calcd for C₁₁H₂₀Si: C, 73.24; H, 11.17. Found: C, 73.37; H, 11.15.

1-Triethylsilylnonyne. Lithio-1-triethylsilylpropyne (50 mmol) in ether was treated with 1-iodohexane (6.23 ml, 40 mmol) in a manner analogous to that described above; the only observable difference was the absence of a precipitate during metallation. Glpc analysis using n-octadecane as internal standard (t_r 12.1 min) showed a single product 13g, 98%, 7.2 min (column H, 150°). Distillation of the crude product through a 30-cm Holtzmann column gave 8.08 g (85%) of 1-triethylsilylnonyne: bp 80-83° (0.15 mm). A pure sample was isolated by preparative glpc (column O, 100°): ir 2193 (s, C≡C), 1451 (s), 1010 (s), 710 cm⁻¹ (s); nmr δ 0.48, 0.51, 0.62, 0.79, 0.82 (m, 6, CH₂-Si), 0.89-1.18 with strong peaks at 0.89 and 1.00 (m, 12, CH₃), 1.27-1.33 (m, 8, n-C₄H₈), 2.24 (m, 2, CH₂-C≡C); mass spectrum parent m/e 238.

Anal. Calcd for C₁₅H₃₀Si: C, 75.54; H, 12.68. Found: C, 75.52; H, 12.56.

A sample of the isomeric allene, 3-triethylsilyl-1,2-nonadiene, was isolated by preparative glpc (column H, 140°) from the reaction carried out in THF: ir 1927 cm⁻¹ (s, C=C=CH₂); glpc t_r 6.3 min (column H, 150°).

trans-1-Triethylsilyl-6,10-dimethylundeca-5,9-diene-1-yne. Lithio-1-triethylsilylpropyne (25 mmol) in ether was treated with freshly prepared geranyl bromide (3.75 ml, 20 mmol) as described above. Glpc analysis using naphthalene as internal standard (t_r 9.2 min) showed three components: 131, 81%, 7.8 min; 141, 6%, 6.9 min; and a third compound, 6%, 5.5 min (column H, 200°). Distillation of the crude product through a 30-cm Holtzmann column yielded 4.61 g (80%) of the title compound as a yellow liquid: bp 109-113° (0.02 mm); ir⁷⁹ 2179 (s, C≡C), 1660 (w, C=C), 1456 (s), 1015 (s), 718 cm⁻¹ (s); nmr δ 0.48, 0.51, 0.62, 0.72, 0.74 (m, 6, CH₂-Si), 0.88-1.29 with strong peaks at 0.88 and 1.00 (m, 9, CH₃ of C₂H₅-Si), 1.62 (s, 6, cis-CH₃), 1.70 (s, 3, trans-CH₃), 2.02-2.29 (m, 8, allylic CH₂), 5.24 (m, 2, CH=C); mass spectrum parent m/e 290. A sample was purified by preparative glpc (column R, 175°).

Anal. Calcd for C₁₉H₃₄Si: C, 78.54; H, 11.79. Found: C, 78.67; H, 12.39. C, 77.70; H, 11.61.

Mol. wt. Calcd for C₁₉H₃₄Si: 290.2430. Found: 290.2427 (high resolution mass spectrometry).

1-Triethylsilyl-4-phenyl-1-butyne. Lithio-1-triethylsilylpropyne (25 mmol) in ether was treated with benzyl bromide (2.38 ml, 20 mmol) as described above. Glpc analysis using diphenylmethane as internal standard (t_r 8.3 min)

(79) The infrared spectrum of the crude product showed a weak absorption attributed to the isomeric allene, 141, at 1934 cm⁻¹.

showed two products: 13h, 75%, 5.3 min and 14h, 3%, 4.4 min (column G, 200°). Distillation of the crude product through a 6-cm Vigreux column yielded 3.48 g (71%) of 1-triethylsilyl-4-phenyl-1-butyne: bp 103-104° (0.04 mm). A pure sample was isolated by preparative glpc (column O, 140°): ir 2179 (s, C≡C), 1451 (s), 1014 (s), 718 (s), 698 cm⁻¹ (s); nmr (# 2) δ 0.46, 0.50, 0.62, 0.69, 0.72 (m, 6, CH₂-Si), 0.85-1.16 with strong peaks at 0.85 and 0.97 (m, 9, CH₃), 2.49, 2.58, 2.71, 2.81, 2.90 (m, 4, CH₂-CH₂), 7.22 (s, 5, phenyl); mass spectrum parent m/e 244.

Anal. Calcd for C₁₆H₂₄Si: C, 78.61; H, 9.90. Found: C, 78.68; H, 9.73.

A sample of the isomeric allene, 3-triethylsilyl-4-phenyl-1,2-butadiene, was also isolated by preparative glpc: ir 1930 cm⁻¹ (s, C=C=C).

1-Trimethylsilyl-3-n-hexyl-1-nonyne. The reaction was carried out as previously described except that 1-trimethylsilylnonyne was used instead of 1-trimethylsilylpropyne; 342 mg (61%) of an oil was isolated which contained one major product according to nmr and glpc analysis. Preparative glpc (column U, 210°) yielded a purified sample of the title compound: ir 2145 (s, C≡C), 1252 (s, Me₃Si), 845 cm⁻¹ (vs, Me₃Si); nmr δ 0.13 (s, 9, Me₃Si), 0.88 (t, 6, CH₃), 1.33 (m, 20, CH₂), 2.28 (broad, 1, CH); mass spectrum parent m/e 280; glpc t_r 3.7 min (column E, 130°).

Anal. Calcd for C₁₈H₃₆Si: C, 77.05; H, 12.93. Found: C, 76.76; H, 13.31. Mol wt. Calcd for C₁₈H₃₆Si: 280.2586. Found: 280.2583 (high resolution mass spectrometry).

c. Conversion to Terminal Acetylenes.

1-Nonyne. i. From 1-Trimethylsilylnonyne. 1-Trimethylsilylnonyne was treated with aqueous ethanolic silver nitrate followed by aqueous potassium cyanide according to the published method.^{50a} A quantitative yield of 1-nonyne was obtained, identical in all respects (ir, nmr, glpc) with an authentic sample. The presence of a small amount of 3-trimethylsilyl-1,2-nonadiene was indicated by the nmr and infrared spectra of the product.

ii. From 1-Triethylsilylnonyne. Cleavage of the triethylsilyl group from 1-triethylsilylnonyne was achieved by the same procedure as that used for 1-trimethylsilylnonyne.^{50a} Triethylsilanol was removed from the crude product by chromatography through a column of Woelm neutral alumina (activity I); elution with petroleum ether gave 1-nonyne (95%), identical in all respects (ir, nmr, glpc) with an authentic sample.

trans-6,10-Dimethylundeca-5,9-diene-1-yne. The trialkylsilyl groups were removed from 1-trimethyl- and 1-triethylsilyl-6,10-dimethyl-undeca-5,9-diene-1-yne as previously described. In each case, trans-6,10-dimethylundeca-5,9-diene-1-yne was obtained in quantitative yield, identical in all respects (ir, nmr, glpc) with an authentic sample.⁸⁰

(80) G. H. Posner, Ph.D. Thesis, Harvard Univ., June, 1968, p. 94.

d. Condensation with Carbonyl Compounds.

1,1-Diphenyl-4-trimethylsilyl-3-butyn-1-ol. Lithio-1-trimethylsilylpropyne (1.6 mmol) in ether was prepared as described previously and treated with benzophenone (291 mg, 1.6 mmol) at 0° for 52 hr. After hydrolysis, extraction with dilute hydrochloric acid, and drying, 456 mg (97%) of 1,1-diphenyl-4-trimethylsilyl-3-butynol was obtained: ir 3620 (w, OH), 2179 (m, C≡C), 1247 (m, Me₃Si), 844 (s, Me₃Si), 696 cm⁻¹ (s, phenyl); nmr δ 0.04 (s, 9, Me₃Si), 2.85 (broad, 1, OH), 3.13 (s, 2, CH₂), 7.28 (m, 10, phenyl); mass spectrum parent m/e 294.

Mol. wt. Calcd for C₁₉H₂₂OSi: 294.1439. Found: 294.1441.

1-Phenyl-4-trimethylsilyl-3-butyn-1-ol. Lithio-1-trimethylsilylpropyne (2.44 mmol) in ether was prepared as described previously and treated with benzaldehyde (0.212 ml, 2.07 mmol) at 0° for 12 hr. The reaction was hydrolyzed, extracted with dilute hydrochloric acid, and dried to yield an oil (quantitative) whose composition was a 2:1 mixture of 4-trimethylsilyl-1-phenyl-3-butyn-1-ol and 2-trimethylsilyl-1-phenyl-2,3-butadien-1-ol. The two alcohols were separated by preparative tlc (5:1 pet.ether-ether). For 1-phenyl-4-trimethylsilyl-3-butyn-1-ol: ir 3700 (m, OH), 2198 (m, C≡C), 1242 (s, Me₃Si), 840 (vs, Me₃Si), 694 cm⁻¹ (s, phenyl); nmr δ 0.09 (s, 9, Me₃Si), 2.47 (d, 2, J = 13 Hz, CH₂), 3.86 (s, 1, OH), 4.63 (t, 1, J = 13 Hz, CH), 7.22 (s, 5, phenyl); mass spectrum parent m/e 218; tlc R_f 0.34 (5:1 pet.ether-ether, vis. E).

Mol. wt. Calcd for $C_{13}H_{18}OSi$: 218.1127. Found:
218.1126 (high resolution mass spectrometry).

For 1-phenyl-2-trimethylsilyl-2,3-butadien-1-ol: ir 3730 (m, OH), 1938 (s, C=C=C), 1239 (s, Me_3Si), 840 (vs, Me_3Si), 696 cm^{-1} (s, phenyl); nmr δ 0.03 (s, 9, Me_3Si), 3.10 (s, 1, OH), 4.47 (d, 2, $J = 5\text{ Hz}$, $CH_2=C$), 5.22 (t, 1, $J = 5\text{ Hz}$, CH), 7.23 (s, 5, phenyl); mass spectrum parent m/e 218; tlc R_f 0.49 (5:1 pet.ether-ether).

Mol. wt. Calcd for $C_{13}H_{18}OSi$: 218.1127. Found:
218.1128 (high resolution mass spectrometry).

If the reaction was performed at -100° , the ratio of alcohols changed from 69:31 to 72:28.

1-Phenyl-4-triethylsilyl-3-butyne-1-ol. Lithio-1-triethylsilylpropyne (2.44 mmol) in ether was treated with benzaldehyde at 0° as described above. Nmr analysis of the crude product (quantitative) indicated a 68:32 mixture of 1-phenyl-4-triethylsilyl-3-butyne-1-ol and 1-phenyl-2-triethylsilyl-2,3-butadien-1-ol: ir 3620 (m, OH), 2165 (s, $C\equiv C$), 1919 cm^{-1} (s, C=C=C); nmr δ 0.34-1.05 (m, 15, C_2H_5-Si), 2.43 (d, $J = 14\text{ Hz}$, $C\equiv C-CH_2$), 3.73 (s, OH), 4.36 (d, $J = 5\text{ Hz}$, $CH_2=C$), 4.53 (t, $J = 14\text{ Hz}$, $\underline{CH}-CH_2$), 5.01 (t, $J = 5\text{ Hz}$, $CH-C=C$), 7.12 (s, phenyl).

4-Trimethylsilyl-3-butyneic Acid. n-Butyllithium (1.0 ml of 1.6 M, 1.6 mmol), TMED (0.25 ml, 1.6 mmol), and 1-trimethylsilylpropyne (180 mg, 1.6 mmol) were stirred at 25° in hexane (5 ml) for 1 hr. The mixture was poured over powdered dry ice via syringe, warmed to room temperature, diluted with

ether, and acidified with a small volume of 3N hydrochloric acid. 101 mg (40%) was obtained of a 2:1 mixture of 4-trimethylsilyl-3-butynoic acid and 2-trimethylsilyl-2,3-butadienoic acid: ir 3080-2540 (broad, COOH), 2193 (m, C≡C), 1942 and 1912 (m, C=C=C), 1724 and 1685 (sh) (s, C=O), 1640 (sh, C=C), 1250 (s, Me₃Si), 846 cm⁻¹ (vs, Me₃Si); nmr δ 0.17 (s, Me₃Si-C≡C), 0.21 (s, Me₃Si-C=C), 3.41 (s, CH₂-C≡C), 4.92 (s, CH₂=C), 11.60 (s, COOH).

e. 1,4-Addition to 2-Cyclohexenone.

1-(1'-Trimethylsilyl-1'-propyn-3'-yl)-2-cyclohexen-1-ol.

Lithio-1-trimethylsilylpropyne (5.0 mmol) in ether was prepared as described above and treated with 2-cyclohexenone (0.39 ml, 4.0 mmol) at -10° for 2 hr. The reaction mixture was hydrolyzed, extracted with dilute hydrochloric acid, and dried to yield 810 mg (97%) of an oil having no appreciable carbonyl or allenic absorptions in its infrared spectrum. A purified sample was obtained by preparative tlc (4:1 pet. ether-ether, 2 dev.): ir 3497 (w, OH), 2160 (m, C≡C), 1255 (s, Me₃Si), 851 cm⁻¹ (vs, Me₃Si); nmr δ 0.16 (s, 9, Me₃Si), 1.76 (m, 4, CH₂-CH₂), 1.93 (m, 2, allylic CH₂), 2.45 (s, 2, propargylic CH₂), 2.57 (s, 1, OH), 5.74-5.80 (m, 2, CH=C); mass spectrum parent m/e 208; tlc R_f 0.48 (4:1 pet. ether-ether, vis. D). An analytical sample was prepared by bulb-to-bulb distillation at 50° (0.03 mm).

Anal. Calcd for C₁₂H₂₀OSi: C, 69.16; H, 9.68. Found: C, 68.78; H, 9.65. Mol. wt. Calcd for C₁₂H₂₀OSi: 208.1283. Found: 208.1283 (high resolution mass spectrometry).

3-(1'-Trimethylsilyl-1'-propyn-3'-yl)-cyclohexanone.

1. In Ether. Lithio-1-trimethylsilylpropyne (5 mmol) in ether (10 ml) was prepared as described above, diluted with ether (20 ml), cooled to -25° , and added via syringe to a suspension of cuprous iodide (476 mg, 2.5 mmol, 0.5 equiv) in ether (5 ml) at -25° , forming a red-brown suspension.⁸¹ After 15 min at -25° , the mixture was treated with 2-cyclohexenone (0.49 ml, 5 mmol) for 10 min at -25° . The reaction was hydrolyzed, filtered, and extracted with dilute hydrochloric acid and dried (sodium sulfate). A measured aliquot was removed from the known total volume of solution and added to n-eicosane (internal glpc standard); glpc analysis (column I, 190°) showed a 20% yield of the title compound 22 (t_r 7.5 min; n-eicosane, t_r 4.2 min). The crude reaction product was separated by preparative tlc on buffered (pH 8) silica gel (1:1 pet.ether-ether). The major component was the 1,2-addition product 23 (553 mg, 55%), identical by ir, nmr and

(81) Color tests for the presence of organolithium compounds were not satisfactory. The Gilman test⁸² with Michler's ketone on this heterogeneous mixture was negative (light yellow-green) after 1-2 min, but the same test on the precursor lithio-1-trimethylsilylpropyne solution required several drops of iodine-acetic acid reagent to give a transient gray-green color which turned deep red-violet upon standing for a few min (not a positive test). The Gilman test on butyllithium required more iodine reagent to give a positive test in the presence of TMED. Lithio-1-trimethylsilylpropyne also failed to give positive results with a second organolithium test involving p-bromodimethylaniline.⁸³

(82) H. Gilman and F. Schulze, J. Amer. Chem. Soc., 47, 2002 (1925).

(83) H. Gilman and J. Swiss, ibid., 62, 1847 (1940).

tlc (R_f 0.58, 1:1 pet.ether-ether) with the product from lithio-1-trimethylsilylpropyne and cyclohexenone in the absence of cuprous iodide. The minor component was the title compound 22 (199 mg, 20%): ir 2160 (m, $C\equiv C$), 1718 (s, carbonyl), 1253 (m, Me_3Si), 850 cm^{-1} (s, Me_3Si); nmr δ 0.16 (s, 9, Me_3Si), 1.86 and 2.28 (maxima of broad unresolved absorption, 11); mass spectrum parent m/e 193 ($M - 15$); tlc R_f 0.35 (1:1 pet.ether-ether, vis. D). A sample was purified by preparative glpc (column U, 210°).

Anal. Calcd for $C_{12}H_{20}OSi$: C, 69.16; H, 9.67. Found: C, 69.76; H, 9.72.

11. In THF. Lithio-1-trimethylsilylpropyne (5 mmol) in ether (10 ml) was added via syringe to cuprous iodide (476 mg, 2.5 mmol, 0.5 equiv) in THF (20 ml) at -20° , immediately producing a deep burgundy solution. After 10 min, the solution was treated with cyclohexenone (0.49 ml, 5 mmol) for 15 min at -20° , with no visible change. The product was isolated and analyzed by glpc as described above, indicating an 11% yield of 1,4-addition. Preparative tlc separated the crude product into two components, 23 (635 mg, 63%) and 22 (73 mg, 7%), each of which was identical to the corresponding compounds isolated in part 1.

General Procedure for Treatment of Lithio-1-trimethylsilylpropyne with Cuprous Salts (See Table V, p 26). Lithio-1-trimethylsilylpropyne in ether was added to a mixture of cuprous salt and n-eicosane (internal glpc standard) in

solvent according to the experimental conditions listed in table V. The copper complex was treated with 2-cyclohexenone (1.5 equiv) as outlined in table V and then hydrolyzed, filtered, extracted with dilute hydrochloric acid, dried, and analyzed by glpc (column I, 190°) to determine the yield of 1,4-addition product. Simultaneous formation of the 1,2-addition product 23 was demonstrated in most cases by ir, nmr, and tlc analyses of the reaction product.

f. Conversion to Carboxylic Acids.

1. Hydroboration. 1-Trimethylsilylnonyne (251 mg, 1.28 mmol) in THF (1 ml) was treated with borane in THF (0.33 ml of 1.3 M, 0.43 mmol) at room temperature for 1 hr; the reaction was treated successively with 3N sodium hydroxide (1 ml) and 30% hydrogen peroxide (0.25 ml) and stirred at room temperature for 30 min. Ether was added, separated from the aqueous layer, extracted with 1N sodium hydroxide, and dried; 152 mg of oil was isolated whose infrared spectrum was very similar to that of starting material. The combined sodium hydroxide solutions were acidified with 3N hydrochloric acid and extracted with ether, yielding 87 mg (43%) of nonanoic acid; amide mp 96-98° [lit.⁸⁴ mp 99°].

Treatment of 1-trimethylsilylnonyne with one molar equivalent of borane in an analogous manner yielded nonanoic

(84) Handbook of Chemistry and Physics, Chemical Rubber Co., 49th ed., 1968. Prepared by procedure in R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," J. Wiley and Sons, N. Y., 1964, p 235.

acid (15%) and a neutral oil whose infrared and nmr spectra suggested saturated silanes.

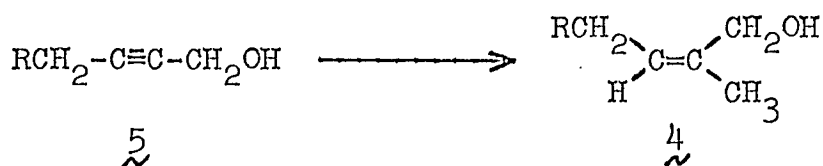
ii. Hydroalumination. 1-Trimethylsilylnonyne (256 mg, 1.30 mmol) and diisobutylaluminum hydride (0.23 ml, 1.30 mmol) were stirred in hexane (1 ml) at room temperature for 16 hr.⁷³ The mixture was treated with ethyl acetate (0.1 ml) at 0° to decompose any excess hydride and then cooled to -78°; oxygen was bubbled into the mixture at -78° for 30 min, while warming to room temperature over a 1 hr period, and at room temperature for 30 min. The reaction was diluted with ether, extracted with 1N sodium hydroxide, and dried to yield 203 mg of oil whose infrared spectrum showed strong hydroxyl and trimethylsilyl absorptions, moderate carbonyl absorption, and weak acetylenic, allenic, and olefinic absorptions. The sodium hydroxide solution was acidified with 3N hydrochloric acid and extracted with ether to yield 76 mg (37%) of nonanoic acid.

CHAPTER 2

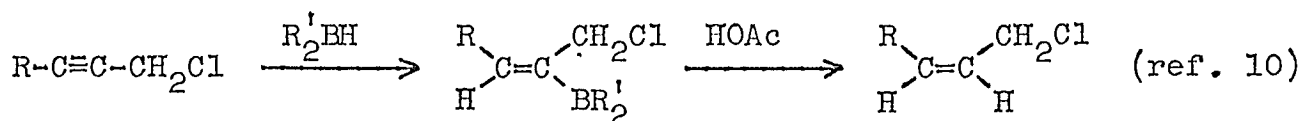
HYDROALUMINATION OF PROPARGYLIC ALCOHOLS TOTAL SYNTHESIS OF α -SANTALOL

A. Introduction.

Reduction of a propargylic alcohol 5 to the allylic alcohol 4 requires a method for cis addition of a hydrogen atom to the β position and some functional element capable of conversion to a carbon-carbon bond to the α position.

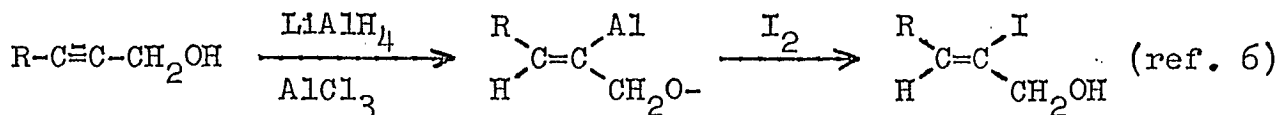


Promising reagents for such a transformation are trivalent boron and aluminum hydrides, which reduce acetylenes by cis addition to vinyl organometallic compounds from which the metal is readily replaced by a variety of functional groups.⁸⁵ Hydroboration of propargylic alcohols and propiolic esters has not been investigated, but regiospecific reduction of a propargylic chloride has recently been reported.¹⁰ Also, aluminum chloride has been used to control the mode of reaction of lithium aluminum hydride with propargylic alcohols.^{6,86}



(85) Reviews: (a) Boron: H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., N. Y., 1962. (b) Aluminum: H. Reinheckel, K. Haage, and D. Jahnke, Organometal. Chem. Rev., Ser. A, 4, 47 (1969).

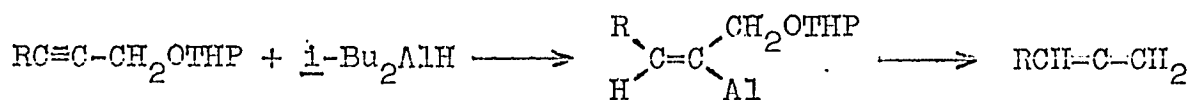
(86) (a) W. T. Borden, Ph.D. Thesis, Harvard University, April, 1968; (b) W. T. Borden and E. J. Corey, Tetrahedron Lett., 313 (1969); (c) J. S. Cowie, P. D. Landor, and S. R. Landor, Chem. Commun., 541 (1969).



Thus, the available evidence indicates that propargylic alcohols may be stereo- and regiospecifically reduced to a convenient precursor of 4.⁴²

B. Hydroalumination of the THP Ether of 2-Decynol.

Treatment of the THP ether of 2-decyn-1-ol with two equivalents of diisobutylaluminum hydride in hexane at 55° yielded 1,2-decadiene in good yield along with recovered starting material. Although addition to the triple bond had



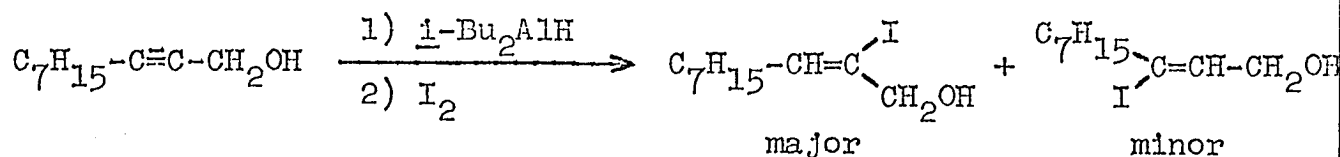
occurred in the desired manner, the intermediate vinylalane was unstable toward elimination.^{86,87} Using diethyl ether as solvent, a mixture of 2-decynol and 2-decenol was obtained, indicating that i-Bu₂AlH may act as a Lewis acid and cleave THP ethers under some reaction conditions. Successful reduction to the THP ether of cis-2-decenol was achieved by addition of a catalytic amount of nickel acetylacetonate,⁸⁸ but a complex mixture of side products was formed as well. From these preliminary results, hydroalumination of THP ethers of propargylic alcohols did not appear promising as a route to 4.

(87) For analogous eliminations, see G. Zweifel and R. B. Steele, Tetrahedron Lett., 6021 (1966); G. Cainelli, F. Bertini, P. Grasselli, and G. Zubiani, ibid., 1581 (1967).

(88) J. J. Eisch and M. W. Foxton, J. Organometal. Chem., 12, P33 (1968).

C. Hydroalumination of 2-Decynol.

Hydroalumination of 2-decynol under a variety of conditions was generally slow and produced mixtures of both cis- and trans- 2-decenol (see table VII). Furthermore, formation of 1,2-decadiene was a competing reaction which was favored by higher reaction temperatures and hydrocarbon solvents, which are less able to solvate the intermediate aluminum complexes. Iodination of the aluminum complex at -78° in ether yielded principally 2-iodo-2-decenol with 3-iodo-2-decenol present as a minor component (about 10%); this isomer distribution is similar to that previously observed^{6c} and will be discussed in more detail later.

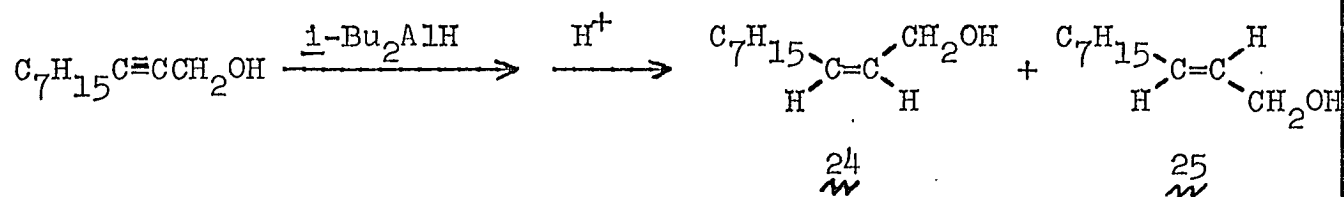


D. Hydroalumination of the Lithium Salt of 2-Decynol.

1. Experimental Results.

When 2-decynol in ether was treated with one equivalent of butyllithium prior to reaction with two equivalents of diisobutylaluminum hydride at 45° for 10-12 hr, trans-2-decenol was formed exclusively upon hydrolysis, as determined by glpc analysis of its trimethylsilyl ether. Iodination of the reaction mixture at -78° yielded principally 2-iodo-trans-2-decenol contaminated by a small amount of 3-iodo-trans-2-decenol; the identity of the two isomers was firmly established by comparison with authentic samples.^{6c} The minor amount of

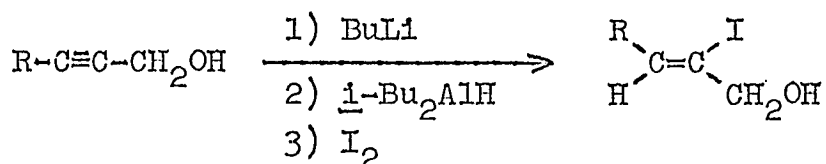
TABLE VII. Hydroalumination of 2-Decynol



Al/Decynol	Additive to Hexane	Temp (°C)	Time (hr)	% Decenol ^a in decenol + decynol	% <u>24</u> ^a in <u>24</u> + <u>25</u>
2	none	55	8	55	74
2	"	25	25	33	
4	"	"	25	43	
"	"	"	60	66	56
2	Ni(AcAc) ₂ ^b	"	2	23	
"	"	"	24	36	
"	"	"	50	26 ^c	62
4	ether	"	1	7	
"	"	"	18	55	
"	"	"	55	77	27
2	"	40	21	67	
3	"	"	21	99	43
6	"	"	20	100	43
2	ether-Ni(AcAc) ₂	25	8	28	
4	"	"	8	45	51
3	THF	60	28	40	20
4	"	25	18	29	0
4	Bu ₂ O	"	19	55	44
4	∅OCH ₃	"	19	46	67
3	" ₃	60	28	60	52
3	∅ ₂ O	"	28	100	56
4	Et ₃ N	25	18	4	32
4	ether alone	"	55	52	25

^a Determined by glpc. ^b Nickel acetylacetonate. ^c Several new peaks observed.

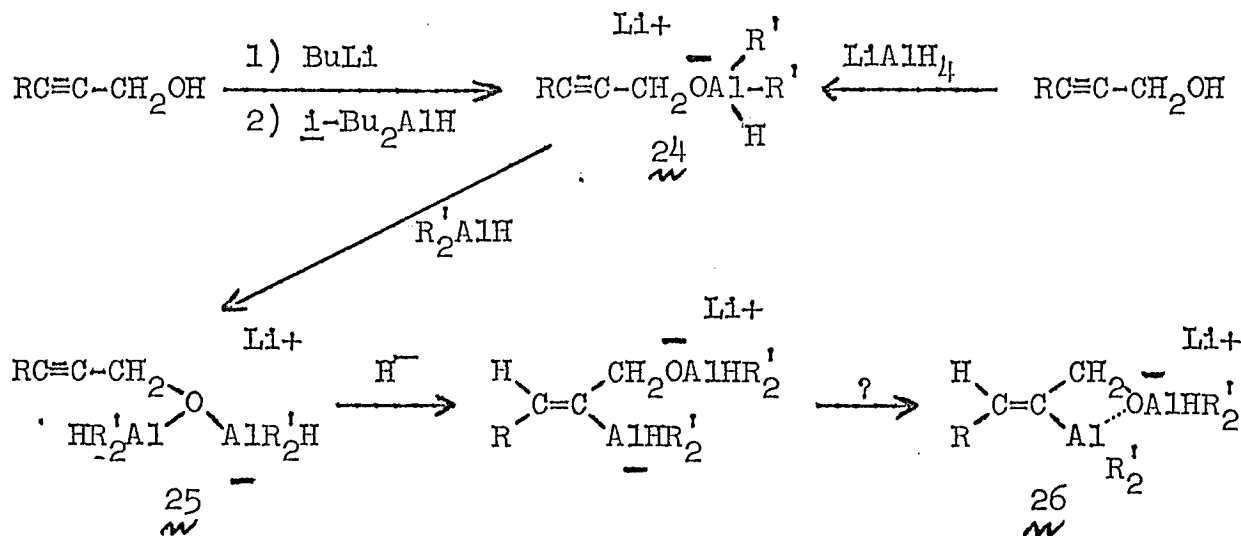
3-iododecenol was completely eliminated when three equivalents of $\underline{i}\text{-Bu}_2\text{AlH}$ were used and the reaction temperature was lowered



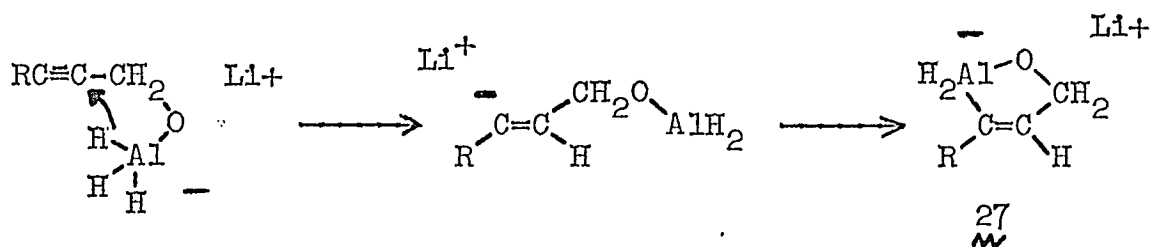
to 35°. This regiospecificity was not observed if sodium hydride replaced butyllithium, LiAlH_4 or AlH_3 replaced $\underline{i}\text{-Bu}_2\text{AlH}$, or THF or DME replaced diethyl ether. Furthermore, reduction was very slow if decynol was added to a complex of butyllithium and $\underline{i}\text{-Bu}_2\text{AlH}$ or if butyllithium was added to a complex of decynol and $\underline{i}\text{-Bu}_2\text{AlH}$. The principal by-product was again 1,2-decadiene, whose yield increased with increasing reaction temperature and longer reaction time.

2. Mechanism of Hydride Reduction.

The initial complex (24) formed during hydroalumination of lithium salts of propargylic alcohols is analogous to that formed in lithium aluminum hydride reductions of propargylic alcohols. Experimentally, the relative proportion of product



derived from hydride addition to C3, increases as the amount of trivalent aluminum hydride in solution increases. It seems reasonable to assume that trivalent aluminum compounds coordinate with the aluminum alkoxide, forming a complex (25) which effectively holds an electrophilic aluminum species near C2, possibly polarizing the triple bond to facilitate hydride addition to C3.⁸⁹ The need for three equivalents of $\underline{1}$ -Bu₂AlH to effect regiospecific reduction and the sole formation of a trans double bond provide some support for this mechanism. In the absence of trivalent aluminum compounds, reduction occurs by intramolecular hydride donation to C2 with subsequent capture of the vinyl carbanion by electrophilic species in solution.⁹⁰ In each case, steric requirements dictate that the oxygen-bound aluminum species can react only at C2.

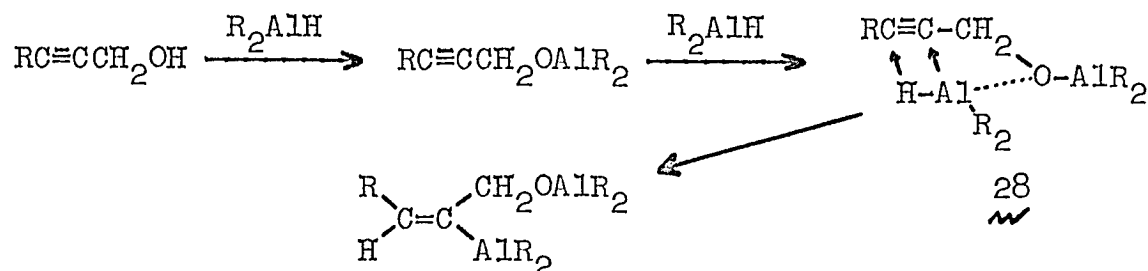


The requirements for regiospecific hydride donation to C3 appear rather strict. Thus, regiospecificity is not observed in THF or DME or from the sodium salt of 24, conditions which favor less-tightly coordinated complexes. Steric

(89) Complexes between trivalent aluminum compounds and isolated double or triple bonds dissociate in ether solvents: G. Hata, *Chem. Commun.*, 7 (1968); J. J. Eisch and C. K. Hordis, *J. Amer. Chem. Soc.*, 93, 2974 and 4496 (1971).

(90) W. T. Borden, *J. Amer. Chem. Soc.*, 90, 2197 (1968); *idem*, *ibid.*, 92, 4898 (1970).

repulsions in 25 should favor migration of one aluminum group from oxygen to carbon. The negatively charged oxygen may also be necessary to coordinate the second aluminum group sufficiently to prevent intramolecular addition of both hydrogen and aluminum, as was found in the reduction of decynol via the uncharged complex 28; such a directed addition is



supported by the high proportion of 2-iodo-2-decenol obtained from reduction and iodination of 2-decynol. Intermolecular hydride addition by the mechanism already discussed most likely accounts for the trans-2-decenol formed from 28. That aluminum hydride in 28 is not as firmly bound as in 25 appears analogous to the significantly greater efficacy of methoxide relative to amines or ethers in directing hydride addition to C2 in LiAlH_4 reductions of propargylic alcohols, in which methoxide was proposed to act as a trivalent aluminum scavenger.^{6c}

It is probable that the stereochemistry of the isolated iodoalcohols truly reflects the stereochemistry of the hydro-alumination process. It has already been demonstrated that cis- and trans-vinylalanes are configurationally stable⁹¹ and that vinylalanes 26 and 27 do not interconvert.^{6c}

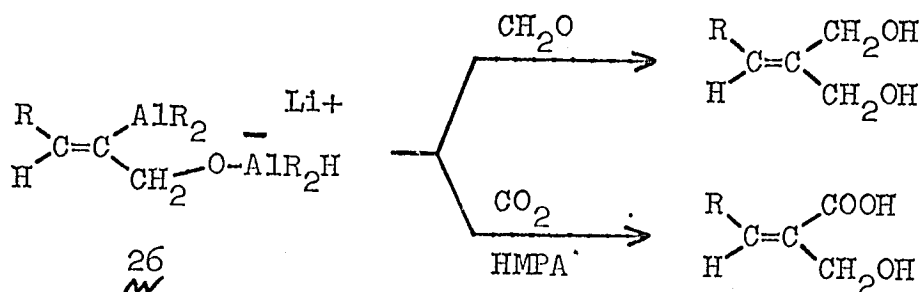
(91) G. Zweifel and R. B. Steele, J. Amer. Chem. Soc., 89, 5085 (1967). The cis-trans isomerizations which have been observed occur by addition and elimination of aluminum hydride: J. J. Eisch and W. C. Kaska, ibid., 88, 2213 (1966).

Furthermore, it is generally accepted that electrophilic substitution of vinylaluminum by iodine occurs with retention of geometric configuration.⁹²

The mechanisms outlined above satisfactorily explain all of the available evidence concerning the reduction of propargylic alcohols by aluminum hydrides; a somewhat different mechanism for intermolecular hydride donation has also been proposed.^{86a}

3. Derivatization of Aluminum Complexes.

Bromination of alane 26 was accomplished by a procedure analogous to that for iodination to yield 2-bromo-trans-2-decenol. Some preliminary experiments were also conducted to replace the vinylaluminum moiety directly with a carbon functional group. Treatment of 26 with paraformaldehyde for 44 hours at room temperature produced the corresponding diol in 34% yield. Carboxylation of 26 was effected if HMPA was added as co-solvent, but methylation by methyl iodide failed even in the presence of HMPA. The low yields realized in

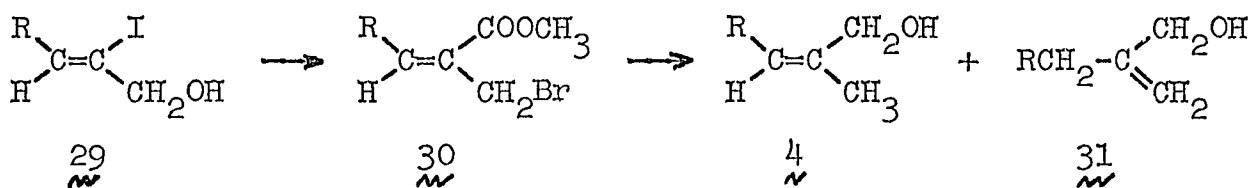


these latter conversions are similar to those found in analogous attempts to alkylate or carbonate the vinylalane from LiAlH_4 reductions of propargylic alcohols.^{6c}

(92) G. Zweifel and C. C. Whitney, J. Amer. Chem. Soc., 89, 2753 (1967).

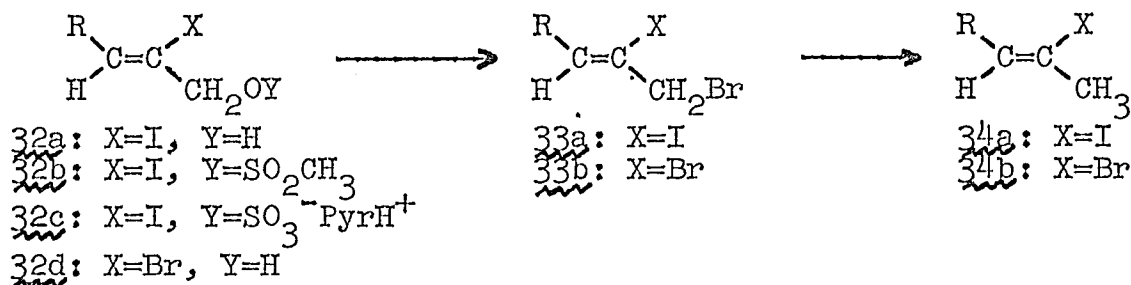
E. Synthesis of Trisubstituted Olefins of Type IV.

Previous work had shown that the elegant three-step conversion of 2-iodo-trans-2-decenol (29) to 2-methyl-cis-2-decenol (4) by hydride reduction of methyl 2-bromomethyl-cis-2-decenoate (30) suffered from the formation of 31 as the major reaction product.^{6c,93} Consequently, a less direct



route to 4 was explored in which the hydroxymethyl group of 29 was transformed to a methyl group before carboxylation.

Conversion of iodoalcohol 32a to iodobromide 33a was readily accomplished by either phosphorus tribromide at 0° in ether⁷⁵ or bromide displacement of the corresponding mesylate 32b; the dibromide 33b was similarly obtained by the action of phosphorus tribromide on 32d. Selective reduction of the allylic halide was effected by sodium borohydride in DMSO at 18° for one hour to produce 34 in high overall yield;⁹⁴ short



(93) See also J. A. Marshall and T. M. Warne, J. Org. Chem., 36, 178 (1971).

(94) R. O. Hutchins, D. Hoke, J. Keogh, and D. Koharski, Tetrahedron Lett., 3495 (1969); H. M. Bell, C. W. Vanderslice, and A. Spehar, J. Org. Chem., 34, 3923 (1969).

reaction periods and cooling were critical in the latter reaction to prevent conversion of the vinyl halide to saturated products.^{95,96} This problem prevented use of iodomesylate 32b, which required nine hours for complete reduction by borohydride and produced mainly saturated products. Borohydride reduction of the bromoester 30 was also tried, but the ester related to 31 was isolated as the principal product.

Several additional but unsuccessful procedures were also tried for converting 32a to 34a. Lithium aluminum hydride reduction of the pyridinium sulfate 32c⁹⁷ led to a mixture of 2-decene and 1,2-decadiene as a result of attack on the vinyl halide.⁹⁸ Lithium aluminum hydride also caused overreduction of dibromide 33b, even at low temperatures.⁹⁹

(95) This same problem has been encountered by other workers who added 1,5-hexadiyne to the reaction to preferentially trap borane: W. S. Johnson, T. J. Brockson, P. Loew, D. H. Rich, L. Werthemann, R. A. Arnold, T. Li, and D. J. Faulkner, J. Amer. Chem. Soc., 92, 4463 (1970).

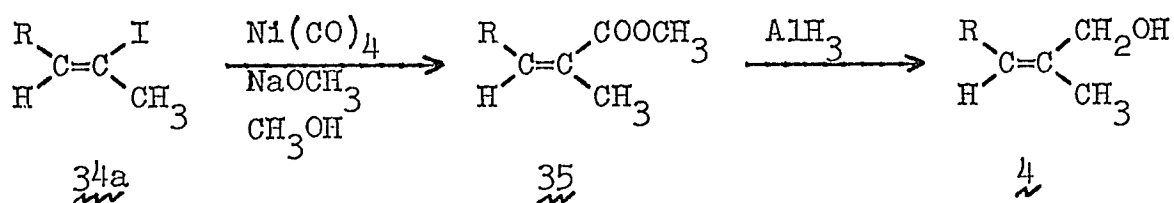
(96) Vinyl and allyl halides have been converted to organoboranes in tetraglyme by sodium borohydride: T. Wartik and R. K. Pearson, J. Inorg. Nucl. Chem., 5, 250 (1958). See also M. F. Hawthorne and J. A. Dupont, J. Amer. Chem. Soc., 80, 5830 (1958); J. F. King, A. D. Allbutt, and R. G. Pews, Can. J. Chem., 46, 805 (1968).

(97) E. J. Corey and K. Achiwa, J. Org. Chem., 34, 3667 (1969).

(98) For analogous examples, see (a) displacement of vinyl halide: L. W. Trevoy and W. G. Brown, J. Amer. Chem. Soc., 71, 1675 (1949); D. J. Burton and F. J. Mettillie, Inorg. Nucl. Chem. Lett., 4, 9 (1968); (b) reductive elimination of vicinal dihalides: J. F. King and R. G. Pews, Can. J. Chem., 42, 1294 (1964).

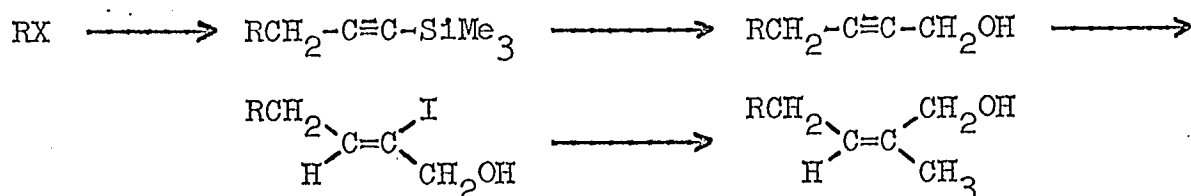
(99) In contrast, the allylic chloride in 33 (X and Br = Cl) may be selectively displaced by LiAlH₄: L. F. Hatch and D. W. McDonald, J. Amer. Chem. Soc., 74, 3328 (1952).

The vinyl iodide 34a was stereospecifically converted to the corresponding methyl ester (35) by nickel carbonyl and sodium methoxide in methanol;¹⁰⁰ in contrast, the vinyl bromide 34b was recovered unchanged after 30 hr. Finally, reduction of the unsaturated ester with aluminum hydride yielded 2-methyl-cis-2-decenol.¹⁰¹ The stereochemistry of



both ester 35 and alcohol 4 was definitively proven by comparison with authentic samples,^{6c} analyzed under conditions which separated the cis and trans isomers.

Formation of 2-methyl-cis-2-decenol (4) from 1-iodohexane by the procedures described in chapters 1 and 2 illustrates a general method for attaching an isoprenoid synthon to a carbon skeleton; the formation of any

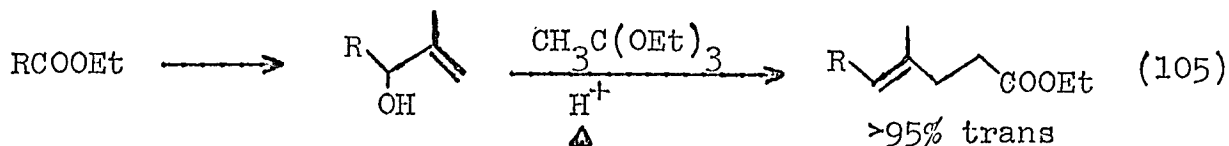
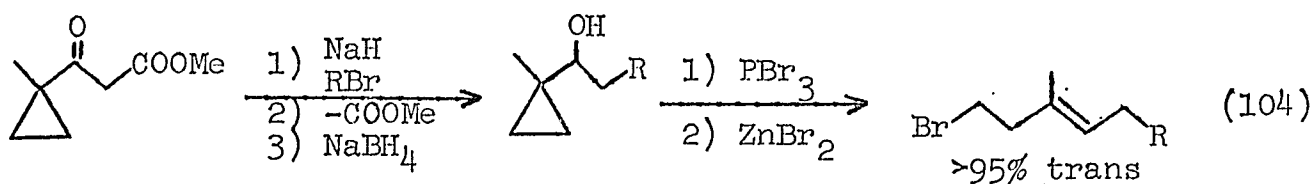
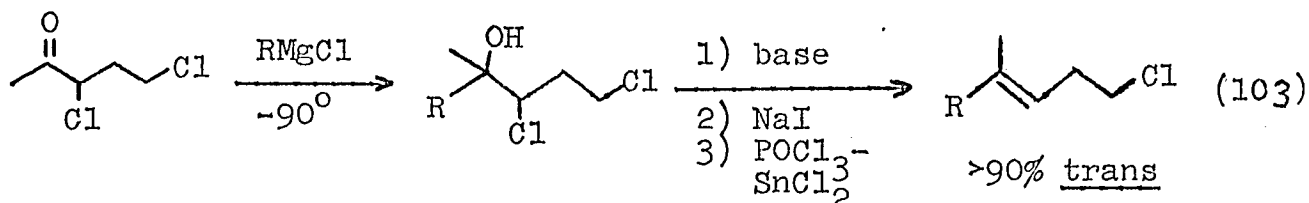


trisubstituted olefin of types 1-4 and the opportunity to repetitiously attach isoprenoid units for building up polyolefinic structures are obvious from the discussion on pp 2-4.

(100) E. J. Corey and L. S. Hegedus, J. Amer. Chem. Soc., 91, 1233 (1969).

(101) M. J. Jorgenson, Tetrahedron Lett., 559 (1962).

Several other methods for extending carbon chains by isoprenoid units have recently been reported which introduce the trisubstituted double bond in a highly stereoselective or stereospecific manner.¹⁰² These rearrangements represent

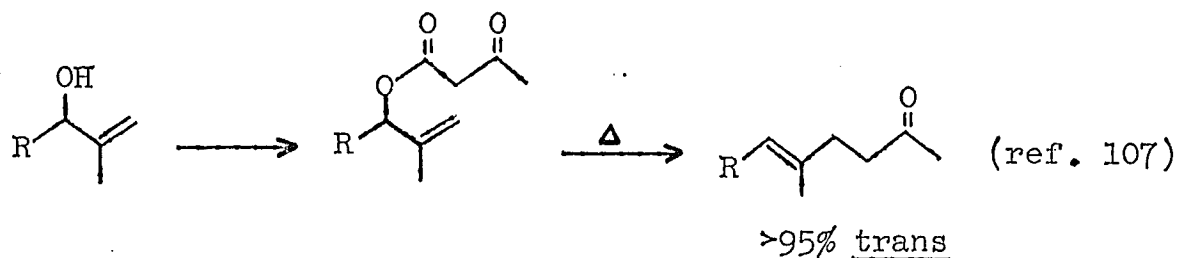
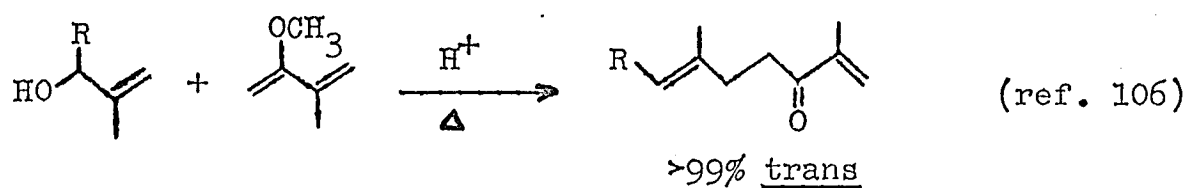


(102) For examples of less stereoselective processes (60-80%), see (a) Wittig reaction: K. H. Dahm, B. M. Trost, and H. Röller, J. Amer. Chem. Soc., 89, 5292 (1967) and (b) Claisen-Cope rearrangement: A. F. Thomas, ibid., 91, 3281 (1969).

(103) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, J. Chem. Soc., 112 and 2539 (1959); the earlier stereoselectivity of >70% was increased to >90% by operating at -90° : S. F. Brady, M. A. Ilton, and W. S. Johnson, J. Amer. Chem. Soc., 90, 2882 (1968).

(104) S. F. Brady, M. A. Ilton, and W. S. Johnson, J. Amer. Chem. Soc., 90, 2882 (1968); W. S. Johnson, T. Li, D. J. Faulkner, and S. F. Campbell, ibid., 90, 6225 (1968). This procedure actually adds a six-carbon unit; chain extension by a five-carbon unit should be possible by rearrangement of the alcohol derived from Grignard addition to 1-methyl cyclopropylcarboxaldehyde.

(105) W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Petersen, ibid., 92, 741 (1970).



extremely efficient methods when applicable, but the stereoselectivity is very sensitive to changes in geometry and substitution patterns and consequently, the reaction can often be used only to synthesize one particular structural type of trisubstituted olefin.¹⁰⁸

F. Stereospecific Total Synthesis of α -Santalol.¹⁰⁹

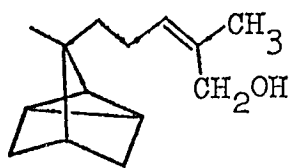
A number of naturally-occurring terpenes are known which possess a trisubstituted double bond of type IV. At the

(106) D. J. Faulkner and M. R. Petersen, Tetrahedron Lett. 3243 (1969); W. S. Johnson, T. J. Brockson, P. Loew, D. H. Rich, L. Werthemann, R. A. Arnold, T. Li, and D. J. Faulkner, J. Amer. Chem. Soc., 92, 4463 (1970); P. Loew and W. S. Johnson, ibid., 93, 3765 (1971); D. J. Faulkner and M. R. Petersen, ibid., 93, 3766 (1971).

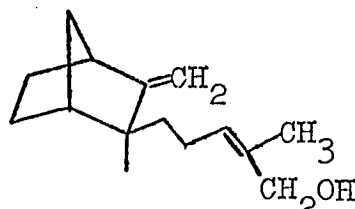
(107) N. Wakabayashi, R. M. Waters, and J. P. Church, Tetrahedron Lett., 3253 (1969).

(108) 2,7-Dimethyl-2,6-octadiene-1,8-diol has recently been introduced as a 10-carbon terpenoid synthon: U. T. Bhallerao and H. Rapoport, J. Amer. Chem. Soc., 93, 5311 (1971).

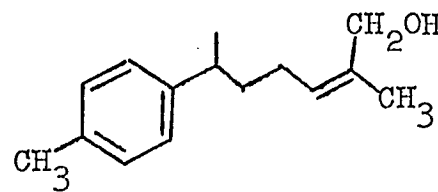
(109) This synthesis of α -santalol has been published: E. J. Corey, H. A. Kirst, and J. A. Katzenellenbogen, ibid., 92, 6314 (1970).



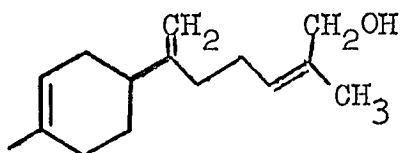
α -Santalol¹¹⁰



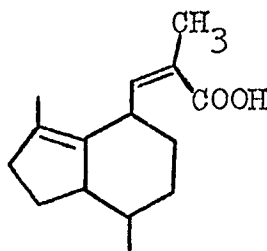
β -Santalol¹¹¹



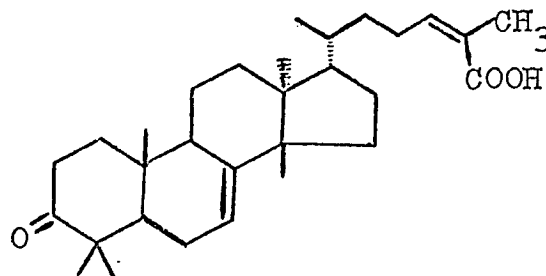
Nuciferol¹¹²



Lanceol¹¹³



Valerenic
Acid¹¹⁴



Masticadienoic
Acid¹¹⁵

outset of this work, no good method for stereospecifically constructing this particular structural unit was known. Recently, a second approach to the synthesis of isoprenoid alcohols of type IV has been published, which utilizes the condensation of a β -oxido phosphonium ylide (36) with paraformaldehyde.^{12c,116}

(110) R. G. Lewis, D. H. Gustafson, and W. F. Erman, Tetrahedron Lett., 401 (1967).

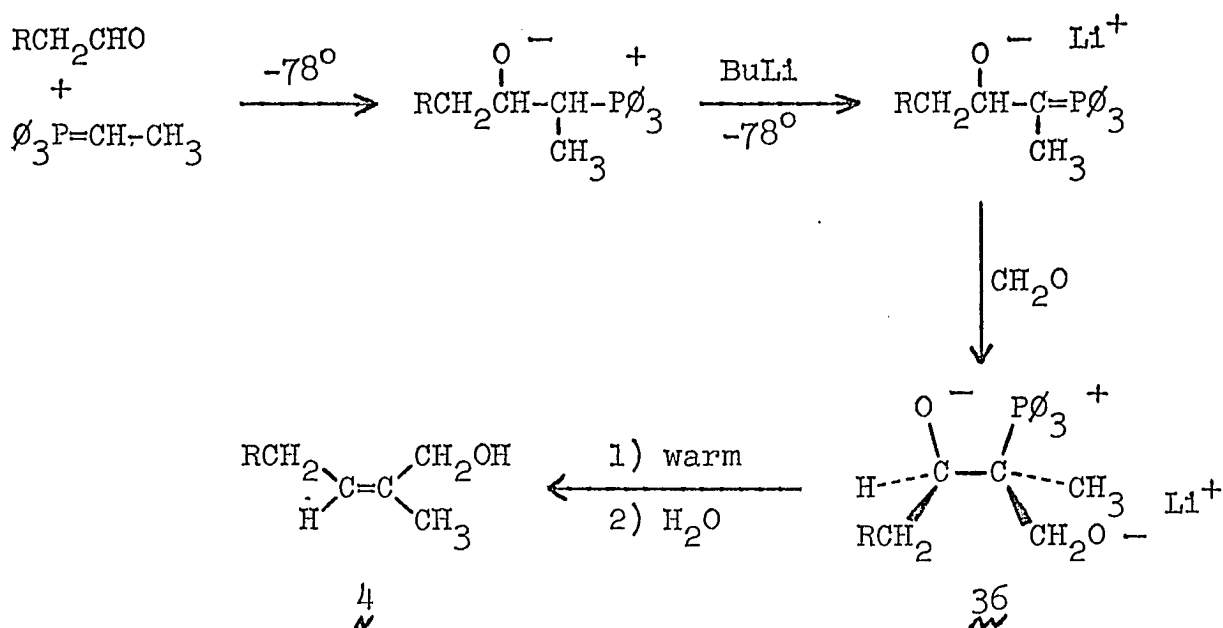
(111) H. C. Kretschmar and W. F. Erman, ibid., 41 (1970).

(112) T. Sakai, K. Nishimura, and Y. Hirose, Bull. Chem. Soc. Japan, 38, 381 (1965); some structures were corrected from an earlier paper in Tetrahedron Lett., 1171 (1963).

(113) A. Manjarrez, T. Riós, and A. Guzmán, Tetrahedron, 20, 333 (1964).

(114) A. Stoll and E. Seebeck, Ann. Chem., 603, 158 (1967).

(115) S. Corsano and E. Mincione, Tetrahedron Lett., 2377 (1965).



α -Santalol (49), an important constituent of East Indian sandalwood oil distilled from the roots and heartwood of Santalum album, possesses a sweet, woody odor which has been valued for centuries as a fragrance.¹¹⁷ Recently, α -santalol, along with β -santalol and bornyl esters, was demonstrated to mimic the natural sex pheromone of the American cockroach, Periplaneta americana.¹¹⁸

Several syntheses of α -santalol have been published,^{110,116,119}

(116) E. J. Corey and H. Yamamoto, J. Amer. Chem. Soc., 92, 226 and 3523 (1970); see also M. Schlosser and D. Coffinet, Synthesis, 380 (1971).

(117) E. Guenther, "The Essentials Oils," Vol. 2, D. Van Nostrand Co., N. Y., 1949, pp 265-269; Vol. 5, 1952, pp 173-187; J. Simonsen and D. H. R. Barton, "The Terpenes," 2nd ed., Vol. 3, Cambridge University Press, Cambridge, England, 1952, pp 178-188.

(118) W. S. Bowers and W. G. Bodenstein, Nature, 232, 259 (1971).

(119) (a) S. Y. Kamat, K. K. Chakravarti, and S. C. Bhattacharyya, Tetrahedron, 23, 4487 (1967); (b) V. M. Sathe, K. K. Chakravarti, M. V. Kadival, and S. C. Bhattacharyya, Ind. J. Chem., 4, 393 (1966); (c) J. Colonge, G. Descotes, Y. Bahurel, and A. Menet, Bull. Soc. Chim. France, 374 (1966).

but in most cases, conventional methods were used to construct the trisubstituted double bond and low yields of the natural cis isomer were obtained.^{110,119} As a result, a stereo-specific synthesis of α -santalol was undertaken to exemplify the procedure for trisubstituted olefin synthesis discussed earlier in this thesis.

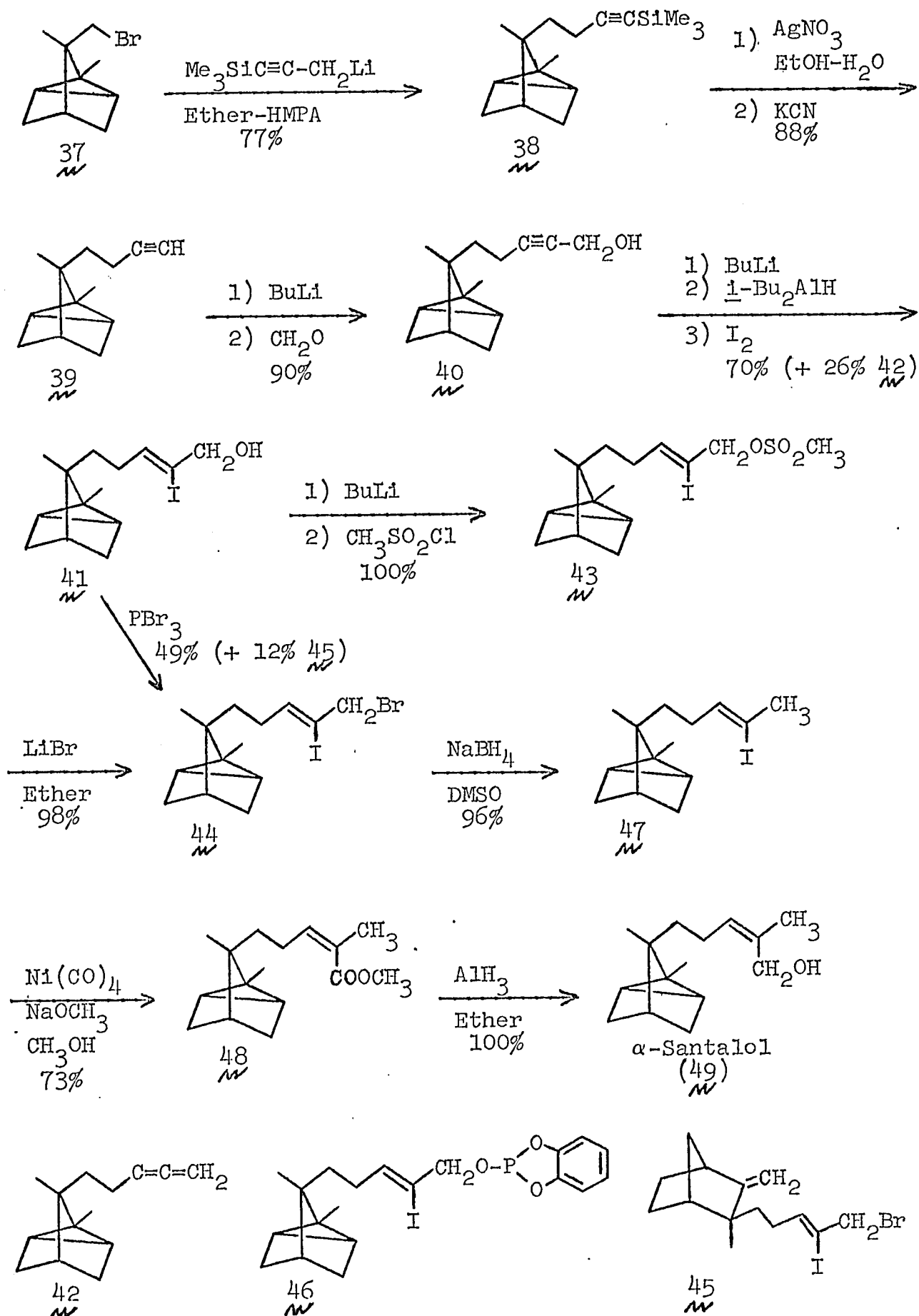
Scheme I illustrates the sequence of reactions employed to convert readily-available π -bromotricyclene¹²⁰ or π -iodotricyclene¹²¹ to α -santalol in an overall yield of 29%. In most cases, the analogous reactions on model compounds have already been described (see pp 16-21 and 57-65) and will not be discussed further. Although lithio-1-trimethylsilyl-propyne did not react with π -iodotricyclene in ether alone, alkylation occurred smoothly upon addition of HMPA.¹²² Treatment of iodoalcohol 41 with phosphorus tribromide in ether led to mixtures of the expected bromide 44 and the rearranged bromide 45 (cf. ref. 119c); this derivative of the β -series (45) undoubtedly arises by an acid-catalyzed cleavage of the cyclopropane ring followed by proton elimination from the tertiary carbonium ion.¹²³ Treatment of phosphite 46 with

(120) E. J. Corey, S. W. Chow, and R. A. Scherrer, J. Amer. Chem. Soc., 79, 5773 (1957).

(121) E. J. Corey, M. Ohno, S. W. Chow, and R. A. Scherrer, ibid., 81, 6305 (1959).

(122) For a review of the solvent properties of HMPA, see H. Normant, Angew. Chem. Int. Eng. Ed., 6, 1046 (1967).

(123) Such rearrangements have been noted previously: see A. Bhati, Perf. Ess. Oil Rec., 53, 15 (1962); idem, J. Org. Chem., 27, 2135 (1962); S. Ramaswami, S. K. Ramaswami, and S. C. Bhattacharyya, J. Org. Chem., 27, 2791 (1962);

SCHEME I. Synthesis of α -Santalol

iodine¹²⁴ likewise caused extensive rearrangement of the tricyclic ring system although the exact products of the reaction were not identified. α -Santalol (49), synthesized as described in scheme I, had infrared and nmr spectra identical with published data^{110,125} and was identical in all respects with a sample prepared by another route.^{116a}

(124) E. J. Corey and J. E. Anderson, J. Org. Chem., 32, 4160 (1967).

(125) I. C. Nigam and L. Levi, Can. J. Chem., 40, 2083 (1962).

G. Experimental Section.

1. Hydroalumination of 2-Decynol and its Derivatives.

1-(2'-Tetrahydropyranyloxy)-2-decyne. Dihydropyran (9.90 ml, 100 mmol) was added to 2-decyne (10.34 g, 67 mmol) and *p*-toluenesulfonic acid (0.86 g, 5 mmol) in ether (25 ml) at 0° and warmed to room temperature after 10 min at 0°. After 2 hr, the ether solution was extracted twice with sodium bicarbonate solution and dried (potassium carbonate). The crude product was dissolved in petroleum ether and passed through a column of basic Alumina III (100 g, 9.5 x 4 cm) to give 15.4 g (97%) of the title compound: ir 2198 cm⁻¹ (vw, C≡C); nmr δ 0.88 (t, 3, CH₃), 1.27 and 1.32 (broad d, 10, n-C₅H₁₀), 1.66 (m, 6, C₃H₆ of THP), 2.23 (m, 2, CH₂-C≡C), 3.60 (m, 2, CH₂O of THP), 4.26 (t, 2, J = 2 Hz, C≡C-CH₂O), 4.83 (m, 1, O-CH-O); glpc t_r 9.3 min (column I, 140°).

1-(2'-Tetrahydropyranyloxy)-*trans*-2-decene. The THP ether of *trans*-2-decenol¹²⁶ was prepared in the manner described above: ir 1675 (w, C=C), 967 cm⁻¹ (s, *trans*-CH=CH); nmr¹²⁷ δ 1.61 (m, 6, C₃H₆ of THP), 1.97 (m, 2, CH₂-C=C), 3.25-4.12 (m, 4, overlapping CH₂O of decenol and THP), 4.61 (m, 1, O-CH-O), 5.63 (m, 2, vinyl); glpc t_r 11.5 min (column L, 140°).

(126) A sample of *trans*-2-decenol prepared by lithium aluminum hydride reduction of 2-decyne was kindly supplied by J. A. Katzenellenbogen.

(127) The nmr absorptions for the n-C₆H₁₃ group were: 0.88 (t, 3, J = 5 Hz, CH₃) and 1.27-1.30 (broad s, 10, n-C₅H₁₀).

cis-2-Decenol. 2-Decynol (0.50 ml, 2.84 mmol) was hydrogenated over 5% palladium-on-barium sulfate (42 mg) in pyridine (10 ml) at atmospheric pressure and room temperature for 20 hr in a semi-micro hydrogenation apparatus.¹²⁸ The reaction was diluted with ether, extracted three times with 3N hydrochloric acid, and dried. 455 mg (quant) of cis-2-decenol was obtained: ir 3520, 3270 (m, OH), 1660 (w, C=C), 1029 cm^{-1} (s, C-O); nmr δ 0.88 (t, 3, CH_3), 1.27 and 1.28 (broad d, 10, $\text{n-C}_5\text{H}_{10}$), 2.00 (m, 2, $\text{CH}_2\text{-C=C}$), 2.80 (s, 1, OH), 4.12, 4.16, 4.20 (m, 2, CH_2O), 5.53 (m, 2, vinyl).

1-(2'-Tetrahydropyranyloxy)-cis-2-decene. The THP ether of cis-2-decenol was prepared in the manner described above: ir 1661 cm^{-1} (w, C=C); nmr¹²⁷ δ 1.63 (m, 6, C_3H_6 of THP), 2.04 (m, 2, $\text{CH}_2\text{-C=C}$), 3.2-4.0 (m, 2, CH_2O of THP), 4.07, 4.16, 4.22 (m, 2, C=C- CH_2O), 4.73 (m, 1, O-CH-O), 5.56 (m, 2, vinyl); glpc t_r 10.3 min (column L, 140°).

Reduction of the THP Ether of 2-Decynol. a. In Hexane. The THP ether of 2-decynol (533 mg, 2.24 mmol) in hexane (5 ml) was treated with diisobutylaluminum hydride (0.80 ml, 4.48 mmol) at room temperature and heated at 55° for 8 hr. The solution was then cooled, quenched with methanol, and filtered; the filtrate was diluted with petroleum ether,

(128) Procedure of W. P. Schneider, cited in L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, John Wiley and Sons, Inc., N. Y., 1967, p 566. See also F. Bohlmann, U. Niedballa, and J. Schneider, Chem. Ber., 98, 3010 (1965).

extracted with dilute hydrochloric acid, and dried (potassium carbonate). The crude product was separated by preparative tlc (pH 8 buffered silica gel, 5:1 pet.ether-ether). The major product was 1,2-decadiene (228 mg, 73%), contaminated by about 8% of 1-decene (glpc analysis): ir 1957 and 845 cm^{-1} (s, $\text{C}=\text{C}=\text{CH}_2$); nmr¹²⁷ δ 1.98 (m, 2, $\text{CH}_2-\text{C}=\text{C}$), 4.67 (m, 2, $\text{CH}_2=\text{C}$), 5.03 (m, 1, $\text{CH}=\text{C}=\text{C}$); glpc t_r 5.6 min (column H, 100°).

122 mg (22%) of starting material was also recovered, identified by infrared spectral and tlc comparison with an authentic sample. The remaining material (65 mg) consisted of a small amount of 2-decynol, identified by its infrared spectrum and tlc properties, along with two unidentified compounds.

b. In Ether. The THP ether of 2-decynol (292 mg, 1.22 mmol) in anhydrous ether (1.5 ml) was treated with diisobutylaluminum hydride (0.65 ml, 3.66 mmol) at room temperature and heated to 35°. Glpc analysis (column I, 140°) of aliquots quenched with 5% sodium hydroxide indicated starting material (t_r 9.3 min) was present after 3 hr but absent after 8 hr; however, no THP ether of 2-decenol was observed (t_r 7.2 min). The reaction was diluted with ether, extracted with 5% sodium hydroxide, and dried (potassium carbonate). 133 mg (about 72%) of a 3:1 mixture (glpc analysis, column A, 150°) of 2-decynol and 2-decenol was isolated.

c. With Nickel Acetylacetonate in Hexane. The THP ether

of 2-decynol (300 mg, 1.26 mmol) and anhydrous nickel acetylacetonate (6 mg, 0.023 mmol) in hexane (2 ml) were treated with diisobutylaluminum hydride (0.23 ml, 1.26 mmol) dropwise at 20° (water bath), immediately forming a deep red-brown solution.⁸⁸ After 2 hr at room temperature, methanol (5 ml) and then water were added and the products were extracted with petroleum ether and dried (potassium carbonate). The THP ether of cis-2-decenol was detected by glpc analysis (column I, 140°) along with a small amount of starting material; a sample collected by preparative glpc (column Q, 125°) was identified as exclusively the cis isomer by comparison (glpc, ir, nmr) with an authentic sample. Tlc analysis of the crude reaction product showed a continuous streak and no solvent system was found which clearly separated any individual component.¹²⁹

Reduction of 2-Decynol. a. General Procedure. 2-Decynol (about 250 mg) dissolved in hexane (1-2 ml) and the particular ether (1 mol per mol of $i\text{-Bu}_2\text{AlH}$) was treated with diisobutylaluminum hydride at 20° and then stirred according to the conditions listed in table VII, p 58. Aliquots were quenched with 3N hydrochloric acid, extracted with ether, dried, and analyzed by glpc (column A, 150°) for the relative proportion of 2-decenol and 2-decynol. After evaporation of

(129) In separate experiments, starting material was completely consumed within 40 min at room temperature, but was incomplete even after 12 hr at 0°.

solvent, a sample of the aliquot in a small volume of anhydrous ether was treated with excess bis(trimethylsilyl)acetamide, shaken for 10 min, and analyzed by glpc (column M, 110°) for the ratio of cis- to trans-2-decenol (t_r 9.6 and 10.2 min respectively for their trimethylsilyl ethers). The results are tabulated in table VII.

b. Product Isolation. 2-Decynol (214 mg, 1.39 mmol) in hexane (2 ml) was treated dropwise with diisobutylaluminum hydride (0.50 ml, 2.78 mmol) at 20° and then heated at 55° for 8 hr. After quenching the reaction with methanol and then water, the mixture was diluted with petroleum ether, extracted with 3N hydrochloric acid, dried, and separated by preparative tlc (4:1 pet.ether-ether, 2 dev.). The least polar component was a mixture of decane, 1- and 2-decene, and 1,2-decadiene (54 mg, about 28%), identified by glpc analysis (column H, 100°). 21 mg (10%) of 2-decynol and 26 mg (12%) of 2-decenol were also isolated and identified by comparison (tlc, ir, nmr, glpc) with authentic samples.

c. Iodination.¹³⁰ 2-Decynol (226 mg, 1.47 mmol) in ether (0.5 ml) and hexane (1.5 ml) was treated dropwise with diisobutylaluminum hydride (0.78 ml, 4.41 mmol) with cooling and then heated to 40° for 21 hr. The reaction was cooled to

(130) The iodination procedure was similar to that described for the iodination of lithium aluminum hydride reduction products (see ref. 3, pp 47-51) with the exception that the iodinated mixture was quenched with thiosulfate without warming to 0°. If warmed to 0°, substantial amounts of the corresponding bis-allylic ethers were formed (see p 80).

0°, treated with ethyl acetate (0.15 ml, 1.5 mmol) to decompose excess hydride, cooled to -78°, and treated with iodine (3.38 g, 13.3 mmol) in ether for 15 min. The reaction was then quenched with basic sodium thiosulfate solution and the product was extracted with ether and dried. The crude product was separated by preparative tlc (5:1 pet.ether-ether, 4 dev.) into two UV-active and one inactive alcohols; the major UV-active component (99 mg, 24%) was 2-iodo-2-decenol, the UV-inactive component (72 mg, 32%) was 2-decenol, and the third component (36 mg) was a mixture of the above two compounds and 3-iodo-2-decenol, all three identified by tlc comparison with authentic samples.^{6c} Although unresolved by tlc, 2-iodo-2-decenol was a mixture of cis and trans isomers, clearly revealed by nmr by the chemical shifts of the vinyl protons: 5.88 (t, J = 6.7 Hz, 2-iodo-trans-2-decenol) and 6.31 (t, J = 7.5 Hz, 2-iodo-cis-2-decenol), in a ratio of about 2.5:1 respectively. The chemical shifts are assigned on the basis of the known deshielding effect of a cis-iodine atom on a vinyl proton¹³¹ and that under the reaction conditions, trans-2-decenol is the dominant isomer after hydrolysis. The 2-decenol isolated from the reaction was also a mixture of cis and trans isomers (nmr analysis).

2-Iodo-trans-2-decenol. n-Butyllithium (5.50 ml of 1.18 M,

(131) S. A. Sherrod and R. G. Bergman, J. Amer. Chem. Soc., 93, 1925 (1971); R. C. Neuman, Jr., and G. D. Holmes, J. Org. Chem., 33, 4317 (1968).

6.50 mmol) and diisobutylaluminum hydride (3.5 ml, 19.5 mmol) were successively added to 2-decynol (1.01 g, 6.50 mmol) in anhydrous ether (6 ml) at -20° , and the colorless solution was heated at 35° for 50 hr. Hydrolysis of an aliquot yielded exclusively trans-2-decenol, identical with an authentic sample and different from cis-2-decenol with regard to infrared and nmr spectra and glpc analysis as its trimethylsilyl ether (column M, 110°). The reaction was quenched with anhydrous ethyl acetate (1.3 ml, 13.0 mmol) at 0° and with iodine (14.8 g, 58.5 mmol) in ether (75 ml) at -78° . After 10 min at -78° , the mixture was poured into basic sodium thiosulfate solution and the product was extracted with ether and dried. The crude product was chromatographed through a column of basic Alumina II (50 g, 22 x 2 cm), eluting with petroleum ether (150 ml), 5:1 pet. ether-ether (90 ml), and ether (200 ml). Evaporation of the ether fraction gave 1.22 g (67%) of 2-iodo-trans-2-decenol, identical in all respects with an authentic sample: ^{6c} ir 3560, 3390 (m, OH), 1650 cm^{-1} (m, C=C); nmr¹²⁷ δ 2.10 (broad t, 2, $J = 7\text{ Hz}$, $\text{CH}_2\text{-C=C}$), 3.20 (s, 1, OH), 4.24 (d, 2, $J = 1.2\text{ Hz}$, CH_2O), 5.92 (t of t, 1, $J = 7$ and 1.2 Hz , vinyl). Tlc analysis (3:1 pet. ether-ether, 2 dev.) showed a single UV-active compound (R_f 0.55) with no trace of the isomeric 3-iodo-trans-2-decenol (R_f 0.49).¹³²

(132) A minor amount of the 3-iodo isomer was observed on tlc analysis if the reduction was performed with two equivalents of diisobutylaluminum hydride at 45° for 10-12 hr.

Evaporation of the petroleum ether chromatography fraction yielded a mixture of isobutyl iodide and 1,2-decadiene, identified by ir, nmr, and glpc analysis.

Bis(2-iodo-trans-2-decen-1-yl) Ether. 2-Decynol (318 mg, 2.06 mmol) was treated successively with n-butyllithium (1.68 ml of 1.23 M, 2.06 mmol) and diisobutylaluminum hydride (1.10 ml, 6.18 mmol) in ether (0.65 ml) at -20° and then heated at 45° for 16 hr. The reaction was quenched with ethyl acetate (0.60 ml, 6.0 mmol) at 0° and iodine (3.05 g, 12 mmol) in ether at -78° and allowed to warm to room temperature; after stirring at room temperature for 15 min to 2 hr, the crude product was isolated as described above and separated by preparative tlc (3:1 pet.ether-ether). In addition to 183 mg (31%) of 2-iodo-trans-2-decenol, 458 mg of a mixture of isobutyl iodide and the title compound was obtained; the structure of the bis-allylic ether was proposed on the basis of its tlc properties and spectral resemblance to 2-iodo-2-decenol: ir no hydroxyl, 1629 (w, C=C), 1155 cm^{-1} (s, C-O); nmr¹²⁷ δ 2.00 (m, 2, $\text{CH}_2\text{-C=C}$), 4.39 (s, 2, CH_2O), 5.90 (t, 1, $J = 6.5$ Hz, vinyl).

2-Bromo-trans-2-decenol. The reduction was carried out exactly as described above except a cold (0°) solution of bromine (3.2 ml, 58.5 mmol) in ether (50 ml) was added at -78° instead of iodine. After chromatography, 1.14 g (75%) of 2-bromo-trans-2-decenol was obtained: ir 3720 and 3450 (m, OH), 1664 cm^{-1} (m, C=C); nmr¹²⁷ δ 2.13 (broad t, 2,

$J = 7$ Hz, $\text{CH}_2\text{-C=C}$), 3.30 (s, 1, OH), 4.21 (broad s, 2, CH_2O), 6.00 (t of t, 1, $J = 7$ and 1.5 Hz, vinyl); mass spectrum parent m/e 234, 236 (doublet). Tlc analysis (3:1 pet.ether-ether, 2 dev.) showed a single compound (R_f 0.55). An analytical sample was obtained by preparative glpc (column R, 135°).

Anal. Calcd for $\text{C}_{10}\text{H}_{19}\text{BrO}$: C, 51.07; H, 8.14; Br, 33.98. Found: C, 50.89; H, 8.09; Br, 34.45. Mol. wt. Calcd for $\text{C}_{10}\text{H}_{19}\text{BrO}$: 234.0615. Found: 234.0620.

2-Hydroxymethyl-2-decenol. 2-Decynol (323 mg, 2.10 mmol) in anhydrous ether (2 ml) was successively treated with n-butyllithium (1.78 ml of 1.18 M, 2.10 mmol) and diisobutylaluminum hydride (1.12 ml, 6.30 mmol) at -20° and then heated at 35° for 46 hr. Anhydrous ethyl acetate (0.6 ml, 6.0 mmol) and a suspension of dry paraformaldehyde (189 mg, 6.30 mmol) in ether (2 ml) were successively added at 0° and the mixture was stirred at room temperature for 44 hr. The colorless solution which had formed was poured into 3N hydrochloric acid and the product was extracted with ether and dried. The crude product was purified by preparative tlc (250:1 ether-methanol) to yield 132 mg (34%) of 2-hydroxymethyl-2-decenol: ir 3320 (s, OH), 1672 (w, C=C), 1016 cm^{-1} (s, C-O); nmr¹²⁷ δ 2.00 (m, 2, $\text{CH}_2\text{-C=C}$), 4.11, 4.21, 4.26 (m, 6, CH_2OH), 5.52 (t, 1, $J = 7$ Hz, vinyl); mass spectrum parent m/e 168 (M - 18); tlc R_f 0.46 (250:1 ether-methanol). Several additional unidentified compounds were present as well as 2-decenol.

2-Hydroxymethyl-cis-2-decenoic Acid and Attempted Methylation of 26. 2-Decynol (344 mg, 2.23 mmol) in ether (2 ml) was treated with n-butyllithium (1.90 ml of 1.18 M, 2.23 mmol) and diisobutylaluminum hydride (1.19 ml, 6.69 mmol) at -20° and then heated at 35° for 48 hr. Anhydrous ethyl acetate (0.7 ml, 7 mmol) was added at 0° and 1.5 ml of the reaction mixture was transferred into another dry, argon-flushed flask. Anhydrous HMPA (2 ml) was added at 0° , carbon dioxide was bubbled into the solution for 5 min, and the solution was stirred under a carbon dioxide atmosphere at 0° for 30 min and at room temperature for 18 hr. The viscous mixture was poured into 3N hydrochloric acid and the product was extracted with ether, then extracted with saturated sodium bicarbonate solution, acidified, re-extracted with ether, and dried. 40 mg (18%) of 2-hydroxymethyl-cis-2-decenoic acid was isolated: ir 3200-2220 (m, COOH and OH), 1698 (s, C=O), 1645 cm^{-1} (m, C=C); nmr¹²⁷ δ 2.57 (m, 2, $\text{CH}_2\text{-C=C}$), 4.29 (s, 2, CH_2O), 6.38 (t, 1, $J = 7$ Hz, vinyl), 7.52 (s, 2, COOH and OH).¹³³

To the original flask was added methyl iodide (0.31 ml, 5 mmol) and anhydrous HMPA (2 ml) at 0° . After 18 hr at 0° , the reaction was diluted with ether, extracted with 3N hydrochloric acid, dried, and analyzed by glpc (column A, 150°); the major product was 2-decenol, with several minor products also present.

(133) No carboxylic acid was isolated if HMPA was not added.

2. Conversion of 2-Iodo-trans-2-decenol to 2-Methyl-cis-2-decenol.

Mesylate of 2-Iodo-trans-2-decenol. 2-Iodo-trans-2-decenol (390 mg, 1.38 mmol) in ether (3 ml) was treated successively with *n*-butyllithium in pentane (1.1 ml of 1.26 M, 1.38 mmol) and methanesulfonyl chloride (0.113 ml, 1.45 mmol) in ether (0.05 ml) at -50° and allowed to warm to -15° over a 30 min period, forming a white precipitate near -20° .¹³⁴ After an additional 30 min at -15° , the mixture was diluted with ether, extracted with sodium bicarbonate solution, and dried. 492 mg (98%) of mesylate 32b was isolated: ir 1645 (w, C=C), 1366 and 1176 cm^{-1} (s, SO_2); nmr¹²⁷ δ 2.12 (m, 2, $\text{CH}_2\text{-C=C}$), 3.07 (s, 3, $\text{CH}_3\text{-SO}_2$), 4.89 (d, 2, $J = 1$ Hz, CH_2O), 6.12 (t of t, 1, $J = 6.5$ and 1 Hz, vinyl); tlc R_f 0.57 (3:1 pet.ether-ether, 2 dev.).

1-Bromo-2-iodo-trans-2-decene.¹³⁵ a. From Mesylate 32b. The mesylate of 2-iodo-trans-2-decenol (39 mg, 0.108 mmol) and lithium bromide (12 mg, 0.135 mmol) were stirred in ether (0.5 ml) at room temperature for 5 hr,¹³⁶ at which point tlc analysis (1:1 pet.ether-ether) indicated complete consumption of starting material. The mixture was diluted with ether, extracted with saturated sodium chloride solution, and dried. 37 mg (100%) of 1-bromo-2-iodo-trans-2-decene

(134) A complex mixture of products was obtained if the additions and reaction were performed at 0° . No advantage was found by cooling to -78° instead of -50° .

(135) For a similar reaction, see G. Stork, P. A. Grieco, and M. Gregson, Tetrahedron Lett., 1393 (1969).

(136) THF could be used as solvent to give a homogeneous reaction, but the results were otherwise the same.

was isolated, pure by nmr analysis: ir 1634 cm^{-1} (m, C=C); nmr¹²⁷ δ 2.08 (m, 2, $\text{CH}_2\text{-C=C}$), 4.34 (s, 2, CH_2Br), 5.97 (t, 1, $J = 7\text{ Hz}$, vinyl).

b. From 2-Iodo-2-decenol and Phosphorus Tribromide.⁷⁵
2-Iodo-trans-2-decenol (309 mg, 1.09 mmol) was treated with phosphorus tribromide (37 μl , 0.39 mmol) in anhydrous ether (2 ml) at 0° for 24 hr in the dark; the reaction was diluted with ether, extracted with sodium bicarbonate solution, and dried. 302 mg (80%) of 1-bromo-2-iodo-trans-2-decene was isolated, identical to that obtained above.

c. From 2-Iodo-2-decenol and Phosphorus Tribromide in the Presence of Calcium Hydride.¹³⁷ Phosphorus tribromide (23 μl , 0.24 mmol) was added to 2-iodo-trans-2-decenol (169 mg, 0.60 mmol) and calcium hydride (25 mg, 0.60 mmol) in hexane (1 ml) at room temperature, causing immediate gas evolution. After 13 hr at 22° , the mixture was diluted with ether, extracted with water, and dried. 140 mg (74%) of 1-bromo-2-iodo-trans-2-decene was isolated, identical to previously obtained samples.¹³⁸

(137) Alcohols containing an acid-sensitive ketal have been successfully converted to the corresponding bromide by phosphorus tribromide in the presence of calcium hydride: see L. Libit, Ph.D. Thesis, Harvard Univ., June, 1970, p. 156; ref. 58a, p. 82.

(138) Analogous reactions in hexane or ether at 0° were incomplete even after 20 hr due to slow conversion of the intermediate phosphite to bromide; the phosphite was characterized by a doublet in its nmr spectrum at 4.70 and 4.86 δ (CH_2O protons split by phosphorus).

1,2-Dibromo-trans-2-decene. 2-Bromo-trans-2-decenol (250 mg, 1.06 mmol) in ether (2 ml) was treated with phosphorus tribromide (38 μ l, 0.40 mmol) at 0° for 24 hr in the dark. The reaction was diluted with ether, extracted with sodium bicarbonate solution, and dried. 264 mg (83%) of 1,2-dibromo-trans-2-decene was isolated: ir 1645 cm^{-1} (m, C=C); nmr¹²⁷ δ 2.12 (m, 2, $\text{CH}_2\text{-C=C}$), 4.25 (s, 2, CH_2Br), 6.13 (t, 1, $J = 7$ Hz, vinyl).

2-Iodo-trans-2-decene. 1-Bromo-2-iodo-trans-2-decene (271 mg, 0.785 mmol) in anhydrous DMSO (3 ml) was added over a 30 min period to sodium borohydride (60 mg, 1.57 mmol) in DMSO (9 ml) at 18° (water bath).^{94, 139} After 1 hr at 18°, the mixture was carefully added to cold 3N hydrochloric acid and the product was extracted with petroleum ether and dried. 196 mg (94%) of 2-iodo-trans-2-decene was isolated: ir 1658 cm^{-1} (m, C=C); nmr¹²⁷ δ 2.02 (m, 2, $\text{CH}_2\text{-C=C}$), 2.47 (m, 3, $\text{CH}_3\text{-C=C}$), 5.41 (t of q, 1, $J_t = 7$ Hz, $J_q = 1.5$ Hz, vinyl); tlc R_f 0.78 (50:1 pet.ether-ether). Glpc analysis (column K, 200°) showed a single peak (t_r 9.6 min).¹⁴⁰

2-Bromo-trans-2-decene. 1,2-Dibromo-trans-2-decene (201 mg, 0.674 mmol) in DMSO (4 ml) was slowly added to sodium

(139) It is very important to perform the addition slowly with external cooling to prevent decomposition.

(140) cis and trans isomers of 2-chloro-2-nonene and 2-iodo-2-nonene have been separated with this column: E. J. Corey, J. I. Shulman, and H. Yamamoto, Tetrahedron Lett., 447 (1970).

borohydride (51 mg, 1.35 mmol) in DMSO (6 ml) as described above, yielding 150 mg (100%) of 2-bromo-trans-2-decene: ir 1667 cm^{-1} (m, C=C); nmr¹²⁷ δ 2.07 (m, 2, CH₂-C=C), 2.27 (d, 2, J = 1.5 Hz, CH₃), 5.60 (t of q, 1, J_t = 6 Hz, J_q = 1.5 Hz, vinyl). Glpc analysis (column K, 180°) showed a single compound (t_r 9.6 min).¹⁴⁰

Reduction of Mesylate 32b. The mesylate of 2-iodo-trans-2-decenol (155 mg, 0.432 mmol) in DMSO (2 ml) was slowly added to sodium borohydride (33 mg, 0.864 mmol) in DMSO (4 ml) as described above; aliquots quenched in dilute acid after 1, 4, and 9 hr indicated that starting material had been consumed after 9 hr, but very little unsaturated product was present judging from the nmr spectrum of the isolated material.

Methyl 2-Bromomethyl-cis-2-decenoate. Methyl 2-hydroxymethyl-cis-2-decenoate^{6c} (102 mg, 0.477 mmol) was treated with phosphorus tribromide (16 μ l, 0.17 mmol) in ether (1 ml) at 0° in the dark for 26 hr. The solution was diluted with ether, extracted with sodium bicarbonate solution, and dried. 128 mg (97%) of methyl 2-bromomethyl-cis-2-decenoate was isolated: ir 1727 (s, C=O), 1645 cm^{-1} (m, C=C); nmr¹²⁷ δ 2.48 (broad t, 2, J = 7 Hz, CH₂-C=C), 3.82 (s, 3, OCH₃), 4.19 (s, 2, CH₂Br), 6.36 (t, 1, J = 7.5 Hz, vinyl).

Reduction of Methyl 2-Bromomethyl-cis-2-decenoate. Methyl 2-bromomethyl-cis-2-decenoate (117 mg, 0.42 mmol) in DMSO (2 ml) was slowly added to sodium borohydride (32 mg, 0.84 mmol) in DMSO (3 ml) as described above. 83 mg (100%)

of product was isolated which consisted of one major component (t_r 5.4 min, 75%) and two minor components (t_r 4.5 min, 10%; t_r 7.4 min, 15%) according to glpc analysis (column I, 100°). The major constituent was separated by preparative glpc (column R, 140°) and identified as methyl 2-methylenedecanoate: ir 1754 (s, C=O), 1661 (w, C=C), 944 and 910 cm^{-1} (m, C=CH₂); nmr¹²⁷ δ 2.33 (broad t, 2, CH₂-C=C), 3.78 (s, 3, OCH₃), 5.56 and 6.17 (two s, 2, C=CH₂);¹⁴¹ mass spectrum parent m/e 198.

Mol. wt. Calcd for C₁₂H₂₂O₂: 198.1620. Found 198.1614 (High resolution mass spectrometry).

Reduction of 2-Iodo-trans-2-decenol with Pyridine-Sulfur Trioxide and Lithium Aluminum Hydride.⁹⁷ 2-Iodo-trans-2-decenol (192 mg, 0.68 mmol) was treated with pyridine-sulfur trioxide complex (162 mg, 1.02 mmol) in anhydrous THF (5 ml) at 0° for 5 hr; since tlc analysis indicated that starting material still remained, additional pyridine-sulfur trioxide (54 mg, 0.34 mmol) was added. After an additional hour at 0°, no starting material remained and a suspension of lithium aluminum hydride (155 mg, 4.08 mmol) in THF (10 ml) was added; the mixture was stirred at 0° for 1 hr and at room temperature for 16 hr, at which point tlc analysis indicated starting material was absent. The reaction was quenched by addition of water (0.28 ml), 15% NaOH (0.28 ml), and water (0.84 ml) at 0°; after 15 min, the mixture was diluted with ether, filtered, and dried. The crude product was filtered through basic

(141) The spectra are different from those of methyl 2-methyl-cis-2-decenoate.^{6c}

Alumina II (3 g), eluting with petroleum ether, to give 76 mg (81%) of a 1.2:1 mixture of trans-2-decene and 1,2-decadiene respectively (nmr analysis); glpc analysis (column H, 80°) confirmed the nmr analysis.¹⁴²

Reduction of 1,2-Dibromo-trans-2-decene by Lithium Aluminum Hydride. a. In THF. 1,2-Dibromo-trans-2-decene (67 mg, 0.225 mmol) in THF (0.5 ml) was treated with lithium aluminum hydride in THF (0.18 ml of 2.6 M, 0.45 mmol) at -60°; after 2 hr, glpc analysis (column I, 120°) of an aliquot quenched in dilute acid indicated starting material had not been consumed, so additional lithium aluminum hydride (0.18 ml of 2.6 M) was added. Starting material was still present after an additional three hours,¹⁴³ so the reaction was warmed to -40° over a 1 hr period. After an additional hour at -40°, reduction was nearly complete. The mixture was carefully quenched with cold dilute acid and the product was extracted with ether. 20 mg of a mixture of 2-decene and a second compound were isolated (nmr and glpc analysis).

b. In Ether. 1,2-Dibromo-trans-2-decene (57 mg, 0.192 mmol) in ether (0.5 ml) was treated with lithium aluminum hydride in ether (0.29 ml of 1.35 M, 0.383 mmol) at 0°;

(142) 2-Decenol was cleanly converted to 2-decene by an analogous procedure after 3 hr at room temperature; 2-iodo-2-decenol reacts more slowly in both formation and hydride reduction of the sulfate ester. The proportion of allene varied considerably in different experiments.

(143) 1-Bromo-2-decene had been completely converted to 2-decene at this point in 95% yield.

aliquots analyzed as described above indicated starting material was present after 3 hr but absent after 6 hr. The reaction was carefully quenched with dilute acid and the product extracted with ether and dried. 22 mg of a complex mixture was obtained (tlc, glpc analysis).¹⁴⁴

Methyl 2-Methyl-cis-2-decenoate. Neat nickel carbonyl (0.16 ml, 1.24 mmol) and 2-iodo-trans-2-decene (55 mg, 0.217 mmol) in methanol (0.25 ml) were added successively to sodium methoxide (34 mg, 0.62 mmol) in anhydrous methanol (1 ml) at room temperature, and the solution was heated at 40° for 2 hr, slowly turning deep red;¹⁰⁰ tlc analysis (50:1 pet. ether-ether) at this point indicated complete consumption of starting material.¹⁴⁵ Iodine in methanol was added at room temperature until the iodine color was permanent for 15 min; the mixture was then diluted with ether, extracted with saturated sodium chloride solution and basic sodium thiosulfate solution, and dried. 42 mg (100%) of methyl 2-methyl-cis-2-decenoate was obtained: ir 1724 (s, C=O), 1653 cm⁻¹ (w, C=C); nmr¹²⁷ δ 1.90 (d, 3, J = 1 Hz, CH₃-C=C), 2.38 (m, 2, CH₂-C=C), 3.73 (s, 3, OCH₃), 5.93 (t of q, 1, J_t = 7 Hz, J_q = 1 Hz,

(144) 1-Bromo-2-decene was converted to 2-decene in 90% yield.

(145) The reaction proceeded very slowly at room temperature.

viny1);¹⁴⁶ mass spectrum parent m/e 198. Tlc analysis (50:1 pet.ether-ether) showed a single compound (R_f 0.28); glpc analysis (column I, 100°) showed a single isomer (t_r 4.5 min).¹⁴⁹ An analytical sample was isolated by preparative glpc (column R, 150°).

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.19. Found: C, 72.58; H, 11.14.

2-Bromo-2-decene and Nickel Carbonyl. Neat nickel carbonyl (0.39 ml, 3.00 mmol) and 2-bromo-trans-2-decene (110 mg, 0.50 mmol) in methanol (1 ml) were added successively to sodium methoxide (81 mg, 1.50 mmol) in anhydrous methanol (4 ml) as described above. Even after heating at 50° for 30 hr, tlc analysis indicated starting material had hardly been consumed. Following the above procedure, 124 mg of yellow oil was isolated, consisting predominantly of starting material and only 5-10% of the desired ester (glpc, ir, nmr analyses).

2-Methyl-cis-2-decenol. Lithium aluminum hydride in

(146) The assignment of cis geometry is supported by published nmr data; see ref. 6c, 147, and 148 and references cited therein. No trace of the trans isomer was observed.

(147) K. C. Chan, R. A. Jewell, W. H. Nutting, and H. Rapoport, J. Org. Chem., 33, 3382 (1968).

(148) B. W. Erickson, Ph.D. Thesis, Harvard Univ., May, 1970, chapter 3.

(149) The cis and trans ethyl esters of 2-methyl-2-decenoate^{6c} were separated under these analytical conditions: cis: R_f 0.44, t_r 7.3 min; trans: R_f 0.33, t_r 10.7 min.

ether (0.57 ml of 1.35 M, 0.766 mmol) was added to anhydrous aluminum chloride (34 mg, 0.256 mmol) in ether (1.5 ml) at 0°, forming a white precipitate. After 15 min at 0°, methyl 2-methyl-cis-2-decenoate (76 mg, 0.383 mmol) in ether (0.5 ml) was added. The mixture was stirred for 30 min at 0°, diluted with ether, quenched with cold 3N hydrochloric acid, separated, and dried, yielding 65 mg (100%) of 2-methyl-cis-2-decenol, identical in all respects with an authentic sample:^{6c} ir 3730, 3410 (m, OH), 996 cm^{-1} (s, C-O); nmr ¹²⁷ δ 1.78 (d, 3, $J = 1$ Hz, $\text{CH}_3\text{-C=C}$), 2.00 (m, 2, $\text{CH}_2\text{-C=C}$), 3.10 (s, 1, OH), 4.12 (s, 2, CH_2O), 5.29 (t, 1, $J = 7.5$ Hz, vinyl).¹⁴⁶ Both tlc (5:1 pet.ether-ether, 3 dev.) and glpc (column A, 150°) analyses showed a single isomer with properties identical with those of the cis isomer (R_f 0.48, t_r 5.5 min) and different from those of the trans isomer (R_f 0.42, t_r 6.1 min).^{6c}

3. Synthesis of α -Santalol.

1-Trimethylsilyl-3-(π -tricyclyl)propyne (38). n -Butyllithium in pentane (22.2 ml of 1.26 M, 28.0 mmol) was freed of solvent in vacuo at 20°. The residue was cooled to -15°, and ether (50 ml), TMED (4.30 ml, 28.0 mmol), and 1-trimethylsilylpropyne (4.32 ml, 28.0 mmol) were successively added. After stirring at -15° for 4 hr, the solution was treated successively at -20° with (-)- π -bromotricyclene¹¹⁸ (3.00 g, 14.0 mmol, $[\alpha]_{\text{D}}^{25} -10.5^\circ$) and anhydrous HMPA (30 ml). After 6 hr at -20°, the reaction mixture was quenched with cold

3N hydrochloric acid, and the product was extracted with ether and dried. The crude product was distilled through a 30-cm Holtzmann column to yield 2.65 g (77%) of 38: bp 74-76° (0.02 mm); ir 2160 (s, C≡C), 1255 (s, Me₃Si), 847 cm⁻¹ (vs, Me₃Si); nmr¹⁵⁰ δ 0.13 (s, 9, Me₃Si); mass spectrum parent m/e 246. Glpc analysis (column H, 190°) indicated the product was about 95% pure (t_r 5.8 min). An analytical sample was obtained by preparative glpc (column R, 140°): [α]²³D +31.7° (c 3.6).

Anal. Calcd for C₁₆H₂₆Si: C, 77.97; H, 10.63. Found: C, 78.22; H, 10.58.

The acetylenic silane was also prepared by the above procedure from lithio-1-trimethylsilylpropyne and 0.6 equiv of (-)-π-iodotricyclene¹¹⁹ ([α]²⁴D -26.4° (c 3.1)) in ether-HMPA at -25° for 1.5 hr.

3-(π-Tricyclyl)propyne (39). Acetylenic silane 38 (2.57 g, 11.5 mmol) in ethanol (12 ml) was added over a 15-min period to a solution of silver nitrate (2.60 g, 15.3 mmol) in ethanol (18 ml) and water (6 ml) at room temperature with vigorous (Hershberg) stirring, immediately forming a dense white precipitate.^{50a} After stirring for 15 min, potassium cyanide (4.9 g, 75 mmol) in water (10 ml) was

(150) The tricyclic skeleton of α-santalol and all of the intermediates leading to it exhibited essentially the same nmr absorptions: δ 0.82 (s, 3, CH₃), 1.00 (s, 3, CH₃), 0.85 (sh), 0.95 (sh), 1.13, 1.29, 1.33, 1.42, 1.46, 1.55, 1.70 (complex pattern, 9, ring and methylene protons), and 1.85-2.35 (complex pattern, 2, allylic protons).

added, quickly dissolving most of the precipitate, and the mixture was stirred for 4 hr. The mixture was poured into water, and the product was extracted with petroleum ether and dried. The crude product was distilled under reduced pressure to yield 1.60 g (88%) of 39: bp 86-89° (12 mm); ir 3290 (m, C≡CH), 2123 cm⁻¹ (w, C≡C); nmr¹⁵⁰ (# 3) δ 1.87-2.31 (complex pattern, 3, overlapping CH₂-C≡CH); mass spectrum parent m/e 174. Glpc analysis (column H, 190°) showed the product was greater than 98% pure (t_r 5.5 min). An analytical sample was obtained by preparative glpc (column R, 100°): [α]_D²³ +32.8° (c 2.7).

Anal. Calcd for C₁₃H₁₈: C, 89.59; H, 10.41. Found: C, 89.59; H, 10.49.

4-(π-Tricyclyl)-2-butyne-1-ol (40). n-Butyllithium in pentane (7.0 ml of 1.26 M, 8.85 mmol) was added dropwise to terminal acetylene 39 (1.54 g, 8.85 mmol) in THF (25 ml) at -78°, and the resulting yellow solution was stirred at -78° for 30 min. A suspension of dry paraformaldehyde (530 mg, 17.7 mmol) in THF (5 ml) was added,¹⁵¹ and the mixture was allowed to warm to room temperature over a 30-min period. The colorless solution was stirred for 1 hr at room temperature, diluted with ether, extracted with saturated sodium chloride solution, and dried. The crude product was distilled to yield 1.62 g (90%) of 40: bp 103-105° (0.03 mm);

(151) A. Schaap, L. Brandsma, and J. F. Arens, Rec. Trav. Chim. Pays-Bas, 84, 1200 (1965).

$[\alpha]_{\text{D}}^{24} +34.5^{\circ}$ (c 4.5); ir 3730 and 3480 (m, OH), 2315 and 2252 cm^{-1} (w, $\text{C}\equiv\text{C}$); nmr¹⁵⁰ δ 2.66 (s, 1, OH), 4.23 (t, 2, $J = 2$ Hz, CH_2O); mass spectrum parent m/e 204 (weak), 189 ($M - 15$). The compound exhibited a single spot (R_f 0.47) on tlc (3:1 pet.ether-ether, 2 dev.) and a single peak (t_r 7.3 min) on glpc analysis (column A, 200 $^{\circ}$).

Mol. wt. Calcd for $\text{C}_{14}\text{H}_{20}\text{O}$: 204.1514. Found: 204.1496 (high resolution mass spectrometry).

2-Iodo-4-(π -tricyclyl)-trans-2-buten-1-ol (41). Propargylic alcohol 40 (1.55 g, 7.60 mmol) in ether (7 ml) at -20 $^{\circ}$ was treated successively with n-butyllithium (6.00 ml of 1.26 M, 7.60 mmol) and diisobutylaluminum hydride (4.05 ml, 22.8 mmol), and the colorless solution was heated at 35 $^{\circ}$ for 48 hr. Excess hydride was decomposed with anhydrous ethyl acetate (1.5 ml, 15 mmol) at 0 $^{\circ}$, and iodine (17.3 g, 68.4 mmol) in ether (100 ml) was added at -78 $^{\circ}$. After 10-15 min at -78 $^{\circ}$, the mixture was quenched with basic sodium thiosulfate solution, and the product was extracted with ether and dried. The crude product was dissolved in petroleum ether and chromatographed on basic Alumina II (70 g, 40- x 2-cm column); the column was eluted with petroleum ether (200 ml), 5:1 pet.ether-ether (120 ml), and ether (200 ml). Evaporation of the ether fraction yielded 1.77 g (70%) of 41: ir 3520 and 3380 (m, OH), 1647 cm^{-1} (m, $\text{C}=\text{C}$); nmr¹⁵⁰ ($\#$ 4) δ 3.12 (s, 1, OH), 4.22 (s, 2, CH_2O), 5.90 (t, 1, $J = 7$ Hz, $\text{CH}=\text{C}$); mass spectrum parent m/e 332. Tlc analysis

(3:1 pet.ether-ether, 2 dev.) showed a single compound (R_f 0.52). A sample was purified by preparative tlc (4:1 pet. ether-ether, 3 dev.) followed by evaporative distillation at 130° (0.01 mm): $[\alpha]^{23}_D -2.9^\circ$ (c 4.4).

Mol. wt. Calcd for $C_{14}H_{21}IO$: 332.0639. Found: 332.0637 (high resolution mass spectrometry).

The petroleum ether eluent was evaporated under reduced pressure and separated by preparative tlc (pet.ether) to yield 371 mg (26%) of 4-(π -tricyclyl)-1,2-butadiene (42): $[\alpha]^{23}_D +28.6^\circ$ (c 4.6); ir 1960 and 846 cm^{-1} (s, allene); nmr¹⁵⁰ δ 4.69 (m, 2, $C=C=CH_2$), 4.90, 5.00, 5.14, 5.22 (m, 1, $\underline{CH=C=CH_2}$); mass spectrum parent m/e 188 (vw), 149 (M - $CH=C=CH_2$); tlc R_f 0.62 (pet.ether).

Mesylate of 2-Iodo-4-(π -tricyclyl)-trans-2-buten-1-ol (43). Iodoalcohol 41 (1.00 g, 3.01 mmol) in ether (6 ml) at -50° was treated successively with n-butyllithium in pentane (2.40 ml of 1.26 M, 3.01 mmol) and methanesulfonyl chloride (0.25 ml, 3.16 mmol) in ether (0.2 ml), and the mixture was allowed to warm to -10° over a 30-min period, forming a white precipitate near -10° . After stirring for an additional 30 min at -10° , the mixture was diluted with ether, extracted with cold sodium bicarbonate solution, and dried. A quantitative yield of mesylate 43 was isolated, essentially pure by nmr analysis: ir 1650 (w, $C=C$), 1370 and 1178 cm^{-1} (vs, SO_2); nmr¹⁵⁰ δ 3.07 (s, 3, CH_3-SO_2), 4.88 (s, 2, CH_2O), 6.12 (t, 1, $J = 7\text{ Hz}$, $CH=C$); tlc R_f 0.55 (3:1 pet.ether-ether, 2 dev.).

1-Bromo-2-iodo-4-(π -tricyclyl)-trans-2-butene (44).

Mesylate 43 (1.24 g, 3.01 mmol) in ether (15 ml) was treated with anhydrous lithium bromide (393 mg, 4.51 mmol) at room temperature for 7 hr, then extracted with saturated sodium chloride solution and dried. 1.16 g (98%) of 44 was isolated, pure by nmr analysis: ir 1634 cm^{-1} (m, C=C); nmr¹⁵⁰ δ 4.36 (s, 2, CH₂Br), 5.99 (t, 1, J = 7 Hz, CH=C); tlc R_f 0.60 (pet. ether, 2 dev.).

2-Iodo-4-(π -tricyclyl)-trans-2-buten-1-ol (41) and PBr₃.

Iodoalcohol 41 (180 mg, 0.54 mmol) in ether (1 ml) was treated with phosphorus tribromide (20.5 μ l, 0.217 mmol) in the dark at 0° for 22 hr,⁷⁵ then extracted with cold sodium bicarbonate solution and dried. The crude product (130 mg, 61%) was a 4:1 mixture (nmr analysis) of iodobromides 44 and 45; tlc analysis (pet. ether, 2 dev.) showed two components with R_f values of 0.60 and 0.46, respectively. The mixture was separated by preparative tlc (pet. ether) to yield 75 mg of 44 and 31 mg of 45. The β -santalene derivative 45 was identified by its spectra: ir 1658 and 1634 (m, C=C), 882 cm^{-1} (s, C=CH₂); nmr δ 1.05 (s, 3, CH₃), 0.83, 1.12, 1.32, 1.59, 1.78, 2.09, 2.70 (maxima of complex pattern, 12, ring and methylene protons), 4.35 (s, 2, CH₂Br), 4.50 and 4.76 (two s, 2, C=CH₂), 5.99 (t, 1, J = 7 Hz, CH=C).¹⁵²

(152) The spectra obtained for 45 showed all the characteristic bands of the β -santalene unit as described for β -santalene itself by M. F. Semmelhack, Ph.D. thesis, Harvard Univ., 1967.

2-Iodo-4-(π -tricyclyl)-trans-2-buten-1-ol and o-Phenylene Phosphorochloridite.¹²² o-Phenylene phosphorochloridite (63 mg, 0.361 mmol) in ether (1 ml) was treated at 0° with pyridine (29 μ l, 0.361 mmol) and iodoalcohol 41 (116 mg, 0.35 mmol), yielding a copious white precipitate. The mixture was stirred at room temperature for 14 hr, filtered through Celite, and evaporated under reduced pressure to yield 150 mg (91%) of the phosphite 46: ir 1645 (w, C=C), 1233 (s, P-O-aromatic), 994 cm^{-1} (s, P-O-aliphatic); nmr¹⁵⁰ δ 4.24 (d, 2, J = 7 Hz, CH_2OP), 5.85 (t, 1, J = 7 Hz, vinyl), 7.06 (m, 4, phenyl).

The phosphite 46 was then treated with iodine (89 mg, 0.35 mmol) in methylene chloride (2 ml) at room temperature for 6 hr; the mixture was diluted with ether, extracted with 5% sodium hydroxide and saturated sodium bisulfite solution, and dried. The nmr spectrum of the product was completely different from those of other intermediates in either the α - or β -santalol series: nmr δ 0.75 (s, 3, CH_3), 0.84 (s, 3, CH_3), 0.90-1.90 with strong maxima at 1.21 (complex m), 2.57 (m, 2), 5.88 (m, 2), 6.05 (m, 2); tlc R_f 0.83 (pet. ether, 2 dev.).

2-Iodo-4-(π -tricyclyl)-trans-2-butene (47). Iodobromide 44 (1.16 g, 2.94 mmol) in anhydrous DMSO (5 ml) was slowly added to sodium borohydride (222 mg, 5.88 mmol) in DMSO (30 ml) at 18° (water bath) over a 1-hr period;⁹⁴ after an additional hour at 18°, the colorless solution was slowly added to cold 3N hydrochloric acid, and the product was extracted

with petroleum ether and dried. Evaporation of solvent yielded 891 mg (96%) of 47: ir 1653 cm^{-1} (m, C=C); nmr¹⁵⁰ (# 5) δ 2.48 (d, 3, $J = 1.5\text{ Hz}$, $\text{CH}_3\text{-C=C}$), 5.42 (t of q, 1, $J_t = 7\text{ Hz}$, $J_q = 1.5\text{ Hz}$, CH=C); mass spectrum parent m/e 316. Tlc analysis (pet.ether, 2 dev.) showed a single compound (R_f 0.60); glpc analysis (column I, 120°) showed a single peak (t_r 7.4 min). A sample was purified by preparative glpc (column R, 185°): $[\alpha]_{\text{D}}^{24} -4.6^\circ$ (c 0.5).

Mol. wt. Calcd for $\text{C}_{14}\text{H}_{21}\text{I}$: 316.0690. Found: 316.0700 (high resolution mass spectrometry).

Methyl α -Santalate (48). Nickel carbonyl (2.33 ml, 18.0 mmol) and vinyl iodide 47 (944 mg, 3.0 mmol) were successively added to sodium methoxide (486 mg, 9.0 mmol) in anhydrous methanol (15 ml) at room temperature, and the solution was heated at $40\text{-}45^\circ$, giving a deep red solution after several minutes;¹⁰⁰ the reaction was followed by tlc analysis (50:1 pet.ether-ether, vis. A). After 10 hr, the reaction was quenched with iodine in methanol at room temperature until the iodine color remained for 15 min, diluted with ether, extracted with saturated sodium chloride solution and basic sodium thiosulfate solution, and dried. The crude product was purified by evaporative distillation at 110° (0.01 mm) to yield 540 mg (73%) of methyl α -santalate: ir 1725 (s, C=O), 1650 cm^{-1} (w, C=C); nmr¹⁵⁰ (# 6) δ 1.87 (d, 3, $J = 1.2\text{ Hz}$, $\text{CH}_3\text{-C=C}$), 3.73 (s, 3, OCH_3), 5.93 (t of q, 1, $J_t = 7.5\text{ Hz}$, $J_q = 1.2\text{ Hz}$, CH=C); mass spectrum parent m/e 248. Tlc analysis (50:1 pet.ether-ether) showed a single

compound (R_f 0.30); glpc analysis (column J, 160°) showed a single peak (t_r 6.5 min). A sample was purified by preparative tlc (50:1 pet.ether-ether, 2 dev.) followed by evaporative distillation at 110° (0.03 mm): $[\alpha]^{23}_D +6.1^\circ$ (c 1.9).

Mol. wt. Calcd for $C_{16}H_{24}O_2$: 248.1776. Found: 248.1777 (high resolution mass spectrometry).

α -Santalol (49). Lithium aluminum hydride in ether (1.20 ml of 1.4 M, 1.67 mmol) was added to anhydrous aluminum chloride (74 mg, 0.557 mmol) in ether (6 ml) at 0° , immediately forming a white precipitate. After 15 min at 0° , methyl α -santalate (207 mg, 0.833 mmol) in ether (0.5 ml) was added. After 30 min at 0° , the mixture was quenched with cold dilute acid, and the product was extracted with ether and dried. 183 mg (100%) of α -santalol was isolated: ir 3730 and 3280 (m, OH), 3085, 2995, 2925 (s, CH), 1675 (w, C=C), 1456 (s), 1374 (m), 1316 (w), 1285 (w), 1163 (w), 1096 (sh), 1079 (m), 1033 (sh), 997 (s, C-O), 969 (w), 934 (m), 905 (w), 875 (w), 849 cm^{-1} (m); nmr¹⁵⁰ (# 7) δ 1.77 (d, 3, $J = 1.2\text{ Hz}$, $\text{CH}_3\text{-C=C}$), 2.79 (s, 1, OH), 4.10 (s, 2, CH_2O), 5.27 (unresolved t, 1, $J = 7\text{ Hz}$, CH=C); ¹⁵³ mass spectrum parent m/e 220. Tlc analysis (3:1 pet.ether-ether, 2 dev.) showed a single compound (R_f 0.47), and glpc analysis (column A, 175°) showed a single peak (t_r 7.7 min).^{153b} A sample was purified by

(153) (a) Identical to published data and different from that for CH_3 and H_{trans} ; ¹¹⁰ (b) identical to a sample previously synthesized.^{116a}

preparative tlc (4:1 pet.ether-ether, 2 dev.) followed by evaporative distillation at 80° (0.02 mm): $[\alpha]_{\text{D}}^{23} +17.5^\circ$ (c 3.3) [lit. natural¹⁵⁴ +17.0°; synthetic¹¹⁰ +18.33°].

Mol. wt. Calcd for C₁₅H₂₄O: 220.1827. Found: 220.1828 (high resolution mass spectrometry).

(154) V. Herout, V. Jarolim, and J. Pliva, Collect. Czech. Chem. Commun., 22, 773 (1957).
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PART II

NEW APPLICATIONS OF NICKEL CARBONYL
IN ORGANIC SYNTHESIS

GENERAL INTRODUCTION
USE OF METAL CARBONYLS IN ORGANIC SYNTHESIS

The study and use of metal carbonyls as reagents for organic synthesis is rapidly expanding as organic chemists realize the potential value of these compounds for performing synthetic operations which may otherwise be accomplished only with difficulty if at all.¹⁵⁵⁻¹⁵⁷ The utility of these metal complexes is due to a number of their physical and chemical properties which allow them to interact with organic molecules in a variety of ways.

Metal carbonyls are readily available and generally stable sources of metals in their lower oxidation states; furthermore, oxidation or reduction to new reactive intermediates can often be performed.¹⁵⁸ Since they are usually soluble in common organic solvents, problems associated with heterogeneous reactions are avoided, and the mild conditions

(155) For recent reviews on the use of metal carbonyls in organic synthesis, see (a) M. Ryang, Organometal. Chem. Rev., Ser. A, 5, 67 (1970); (b) M. Ryang and S. Tsutsumi, Synthesis, 55 (1971); (c) E. W. Abel and F. G. A. Stone, Quart. Rev. (London), 24, 498 (1970) and table of reviews cited therein; (d) I. Wender and P. Pino, ed., "Organic Synthesis via Metal Carbonyls," Wiley-Interscience, N. Y., 1968; (e) C. W. Bird, "Transition Metal Intermediates in Organic Synthesis," Academic Press, London, 1967.

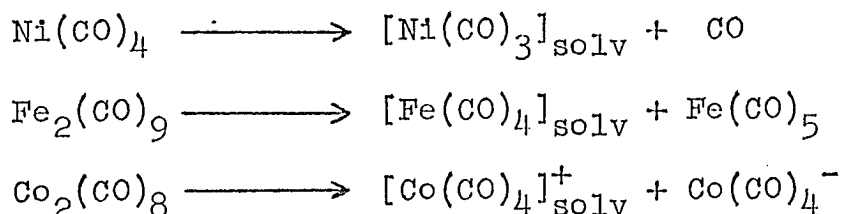
(156) M. F. Semmelhack, Ph.D. Thesis, Harvard University, March, 1967.

(157) L. S. Hegedus, Ph.D. Thesis, Harvard University, March, 1970.

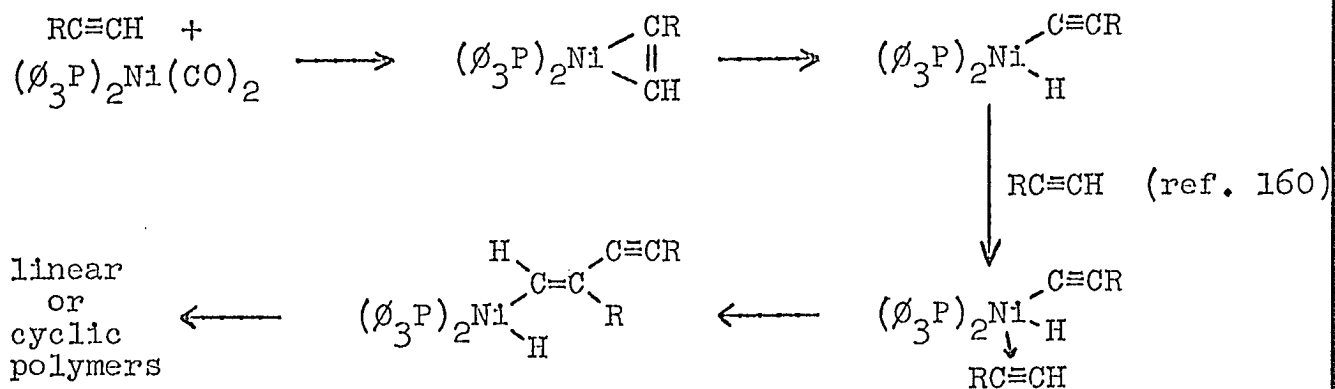
(158) (a) Anionic complexes: R. B. King, Acc. Chem. Res., 3, 417 (1970); (b) Cationic complexes: E. W. Abel and S. P. Tyfield, Adv. Organometal. Chem., 8, 117 (1970); (c) Oxidative addition: J. P. Collman and W. R. Roper, ibid., 7, 53 (1968); J. P. Collman, Acc. Chem. Res., 1, 136 (1968).

under which many reactions are carried out often allow the presence of functional groups in the organic substrate. In many cases, reactions involving metal carbonyls can be made catalytic, a condition which is valuable for industrial synthesis.

From either dissociation of carbon monoxide or cleavage of polynuclear species, coordinatively unsaturated metal complexes are formed which may then coordinate with organic



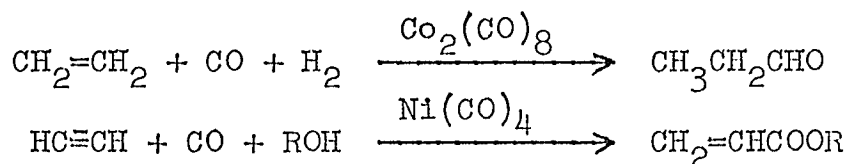
compounds containing unsaturated or polar functional groups; the initially formed complex may be a transient intermediate which undergoes further reaction. The metal complex may function as a template on which carbon-carbon bonds form in a very specific manner.¹⁵⁹



(159) See, for example, G. P. Chiusoli, Aspects of Homogeneous Catalysis, 1, 78 (1970); *idem*, Bull. Soc. Chim. France, 1139 (1969); G. Wilke, Proc. Welch Found., 9, 165 (1965); G. Wilke, *et. al.*, Angew. Chem. Int. Eng. Ed., 5, 151 (1966).

(160) L. S. Meriwether, M. F. Leto, E. C. Colthup, and G. W. Kennerly, J. Org. Chem., 27, 3930 (1962).

The incorporation of carbon monoxide into organic compounds may also occur, either via direct nucleophilic attack on metal-bound carbon monoxide¹⁶¹ or migratory insertion of carbon monoxide into carbon-metal bonds;¹⁶² both carbonylation and carboxylation are possible, as illustrated respectively by the commercially important hydroformylation of olefins (Oxo reaction) and Reppe synthesis of acrylic acids.¹⁶²



Since novel synthetic transformations involving metal carbonyls are continually being reported, it is apparent that these organometallic compounds will become increasingly popular and useful reagents.

Some new synthetic applications of reactions involving nickel carbonyl are reported in the second part of this thesis. The synthesis of a macrocyclic lactone by intramolecular cyclization of an α,ω -diallylic halide and the conversion of diallylic sulfates to 1,5-hexadienes is discussed in chapter three. In chapter four, an approach to the synthesis of cyclopentenones is explored involving cyclization of certain 1,4-diketones generated by 1,4-addition of acylnickel complexes to α, β -unsaturated ketones.

(161) See, for example, the preparation of metal-carbene complexes: E. O. Fischer and A. Maasböl, Chem. Ber., 100, 2445 (1967).

(162) J. Falbe, "Carbon Monoxide in Organic Synthesis," Springer, Berlin, 1970; references 155d and 155e.

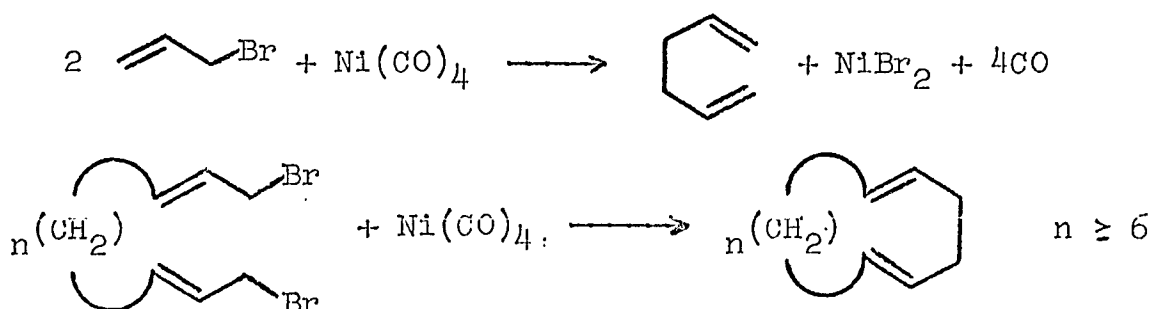
CHAPTER 3
ALLYLIC COUPLING REACTIONS USING NICKEL CARBONYL

A. Formation of Macrocyclic Lactones.

1. Nickel Carbonyl with Esters and Allylic Halides.

Nickel carbonyl has long been known to promote the coupling of allylic halides to 1,5-hexadienes in polar media.^{163,164}

A particularly useful application of this coupling reaction has been the synthesis of a number of macrocyclic hydrocarbons from the appropriate acyclic α,ω -diallylic halides.¹⁶⁵

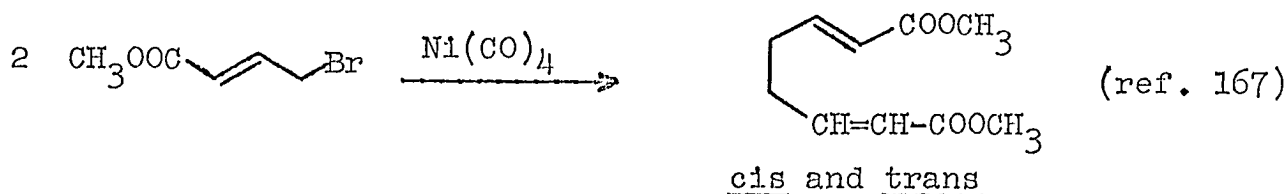
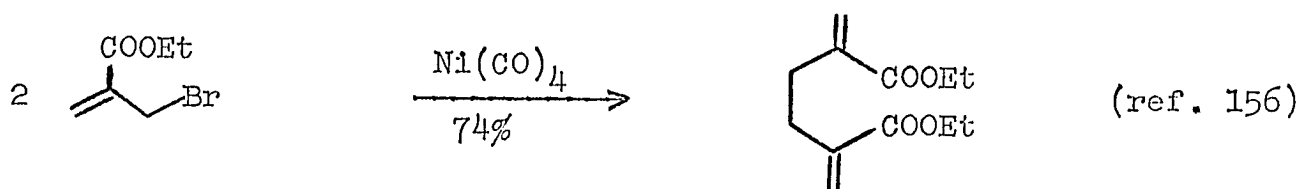
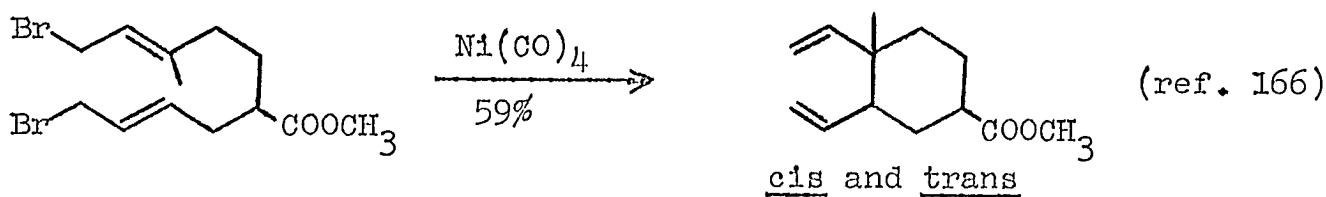


Synthesis of a macrocyclic lactone by such a cyclization process was anticipated since esters are frequently formed in reactions involving nickel carbonyl and are quite stable under the reaction conditions. Furthermore, coupling of allylic halides containing ester functions has been demonstrated in several instances.

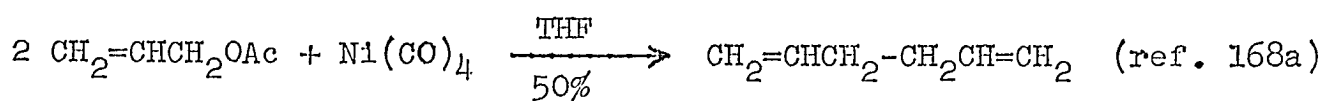
(163) (a) Belg. Pat. 448,884 (1943); Chem. Abstr., 41, 6576 (1947); (b) I. D. Webb and G. T. Borchardt, J. Amer. Chem. Soc., 73, 2654 (1951).

(164) For recent reviews of reactions between nickel carbonyl and unsaturated halides, see P. Heimbach, P. W. Jolly, and G. Wilke, Adv. Organometal. Chem., 8, 29 (1970) and reference 157.

(165) (a) E. J. Corey and E. K. W. Wat, J. Amer. Chem. Soc., 89, 2757 (1967); (b) E. J. Corey and E. Hamanaka, ibid., 86, 1641 (1964); idem, ibid., 89, 2758 (1967); (c) E. J. Corey and M. F. Semmelhack, Tetrahedron Lett., 6237 (1966).



Esters adjacent to double bonds are a particular exception; allylic acetates react, although somewhat less readily, with nickel carbonyl in a manner analogous to that of allylic halides,¹⁶⁸ while methyl 4-bromocrotonate is dehalogenated in hydroxylic solvents and is less readily carboxylated than are simple allylic halides.^{167,169}

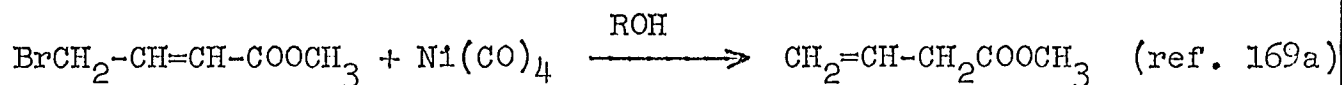


(166) E. J. Corey and E. A. Broger, Tetrahedron Lett., 1779 (1969).

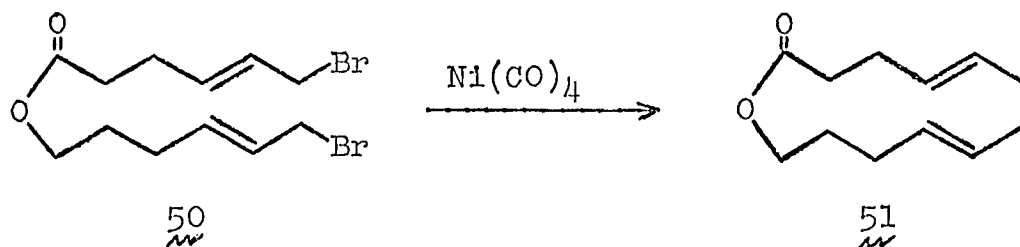
(167) G. P. Chiusoli and L. Cassar, Angew. Chem. Int. Eng. Ed., 6, 124 (1967).

(168) (a) N. L. Bauld, Tetrahedron Lett., 859 (1962); (b) G. P. Chiusoli and S. Merzoni, Chim. Ind. (Milan), 45, 6 (1953); (c) J. B. Mettalia, Jr., and E. H. Specht, J. Org. Chem., 32, 3941 (1967).

(169) (a) dehalogenation: G. Chiusoli, G. Bottaccio, and A. Cameroni, Chim. Ind. (Milan), 44, 131 (1962); (b) carboxylation: L. Cassar and G. P. Chiusoli, Tetrahedron Lett., 3295 (1965).

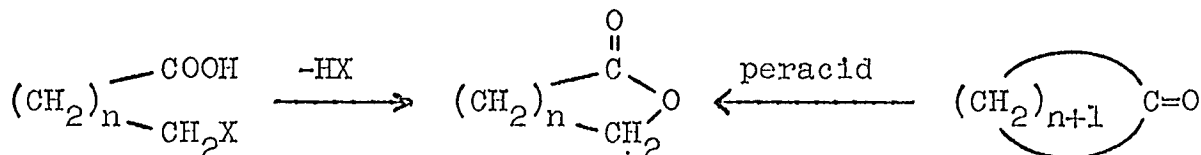


It was thus expected that cyclization of the dibromoester 50 would establish a new and general method for the synthesis of macrocyclic lactones.



2. Synthesis and Importance of Macrocyclic Lactones.

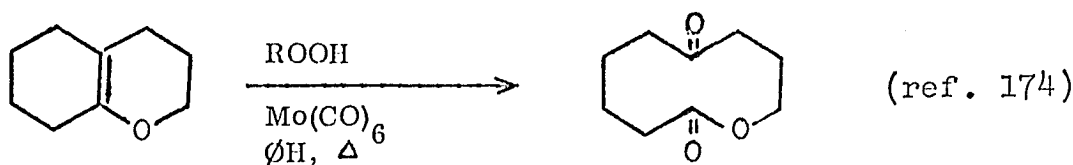
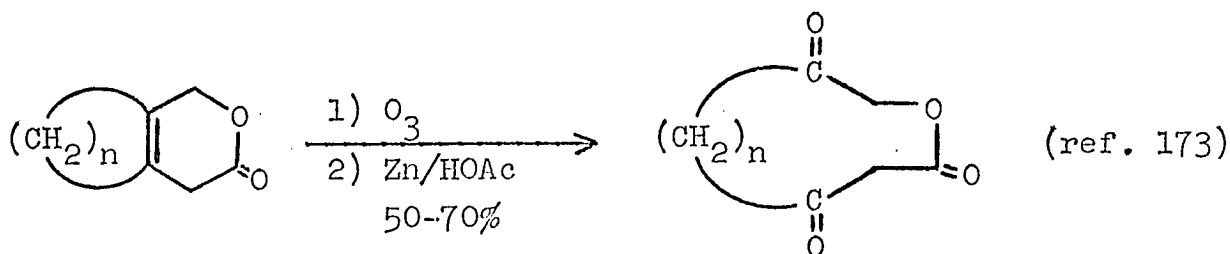
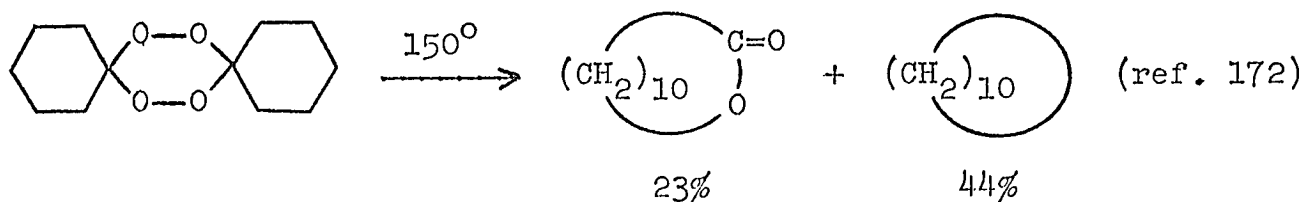
Only a relatively few procedures for constructing large ring lactones are known;¹⁷⁰ the acyloin condensation, commonly used for preparing macrocyclic compounds, cannot be used due to the reactivity of the ester function. Syntheses by classical methods formed the ester linkage as the final step, either by cyclization of ω -hydroxy- or halocarboxylic acids under conditions of high dilution or by Baeyer-Villiger oxidation of cyclic ketones.¹⁷¹ Other transformations of



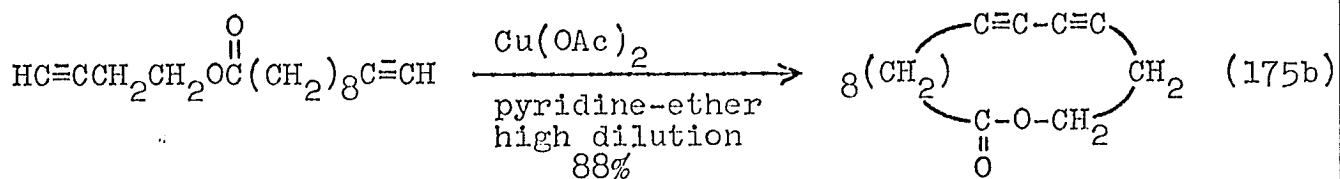
cyclic precursors to macrocyclic lactones have been achieved by rearrangement of cyclic peroxides and cleavage of bicyclic compounds.

(170) For a review of methods for the synthesis of macrocyclic compounds in general, see L. I. Belen'kii, Russ. Chem. Rev., 33, 551 (1964).

(171) P. Z. Bedoukian, "Perfumery Synthetics and Isolates," D. Van Nostrand Co., N. Y., 1951, pp 325-339.



One method for closing the macrocyclic ring via carbon-carbon bond formation has been developed, utilizing the well-known coupling reactions of terminal acetylenes.¹⁷⁵ The



nickel carbonyl-promoted cyclization reported in this chapter adds a new procedure to the relatively small number of methods

(172) P. R. Story, D. D. Denson, C. E. Bishop, B. C. Clark, Jr., and J.-C. Farine, J. Amer. Chem. Soc., **90**, 817 (1968); P. Busch and P. R. Story, Synthesis, 181 (1970).

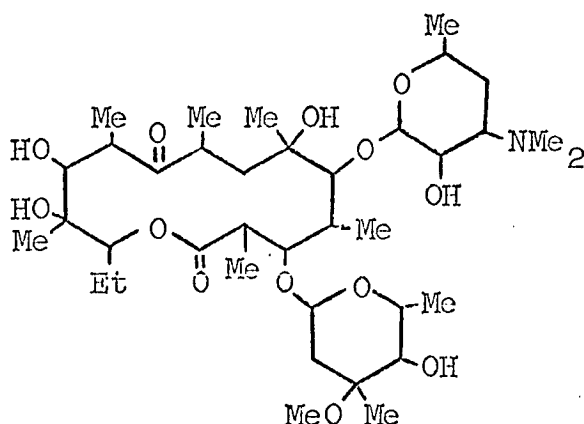
(173) J. Falbe and F. Korte, Chem. Ber., **96**, 919 (1963).

(174) R. D. Rapp and I. J. Borowitz, Chem. Commun., 1202 (1969).

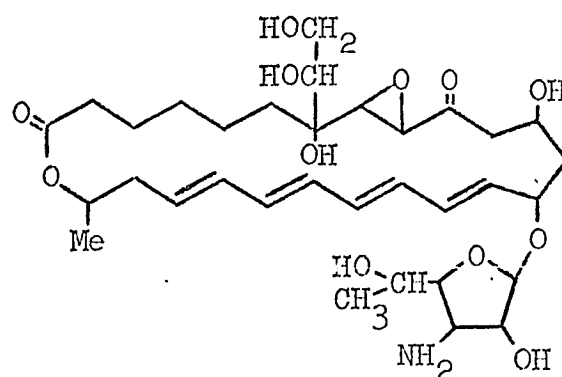
(175) (a) G. Eglinton and A. R. Galbraith, J. Chem. Soc., 889 (1959); (b) J. Carnduff, G. Eglinton, W. McCrae, and R. A. Raphael, Chem. Ind. (London), 559 (1960); (c) L. D. Bergelson, J. G. Molotkovsky, and M. M. Shemyakin, ibid., 558 (1960); idem, J. Gen. Chem. USSR, **32**, 57 (1962).

available for the synthesis of macrocyclic lactones.

Large ring lactones have long been valued as perfumery agents; lactones with fourteen to seventeen atoms in the ring possess musk-like odors.¹⁷⁶ More recently, numerous compounds with antibiotic properties have been isolated from various strains of Streptomyces and shown to contain a highly substituted, sometimes polyunsaturated, macrocyclic lactone, often linked glycosidically to unusual sugar molecules.^{177,178}



Erythromycin



Pimaricin

Known as macrolides,^{177a} this relatively new class of medicinally important compounds unquestionably poses an extremely complex synthetic challenge.

(176) E. Guenther, "The Essential Oils," Vol. 2, D. Van Nostrand Co., N. Y., 1952, p 489.

(177) Reviews: (a) R. B. Woodward, Angew. Chem., 69, 50 (1957); (b) M. Berry, Quart. Rev. (London), 17, 343 (1963); (c) R. M. Evans, "The Chemistry of the Antibiotics Used in Medicine," Pergamon Press, Oxford, England, 1965, pp 135-173.

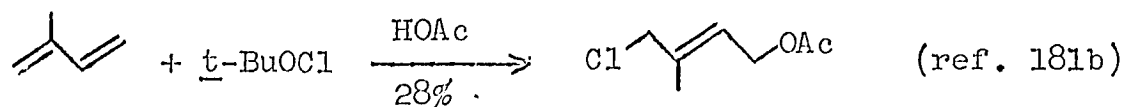
(178) The role of macrolides within the producing organism is unclear; a relationship between them and polycyclic compounds has been postulated.^{177b} Recently, it has been proposed that macrolides serve to detoxify abnormal sugars and other toxic compounds produced by the organism.¹⁷⁹

(179) M. M. Dhar and A. W. Khan, Nature, 233, 182 (1971).

3. Synthesis of 12-Hydroxy-4,8-dodecadienoic Acid Lactone.¹⁸⁰

The synthetic sequence leading to 12-hydroxy-4,8-dodecadienoic acid lactone (51) is outlined in scheme II on p 110; the overall strategy involved formation of an ester with a terminal O-protected allylic alcohol (55) from which could be constructed an acyclic ester containing a protected allylic alcohol at each end of the chain (59). Cyclization of the α, ω -diallylic bromide (50) by nickel carbonyl following established procedures¹⁶⁵ would then yield the desired lactone.

A convenient starting material was a derivative of 2-butene, 1,4-unsymmetrically disubstituted in such a way that a two-carbon terminal ester function would displace one substituent while leaving an allylic alcohol precursor at the opposite end of the disubstituted butene. The preparation of such disubstituted butenes in high yield has presented problems in the past; 1,4-addition to butadiene and allylic bromination of crotyl derivatives suffer from concurrent 1,2- and 1,4-addition,¹⁸¹ while monosubstitution of 1,4-dibromobutene or 1,4-butanediol cannot be made quantitative.

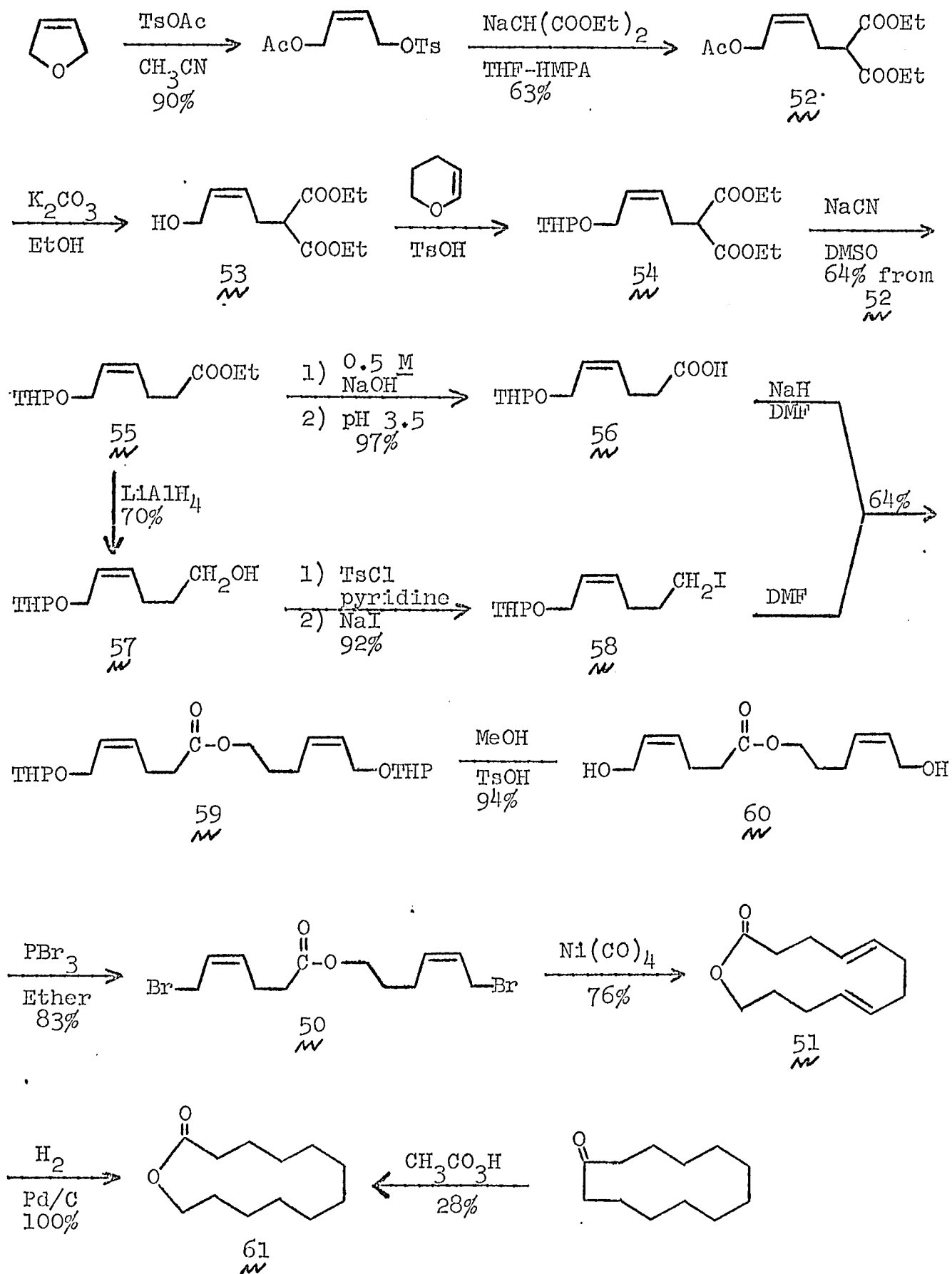


Very recently, however, 1-tosyloxy-4-acetoxy-2-butene

(180) E. J. Corey and H. A. Kirst, submitted for publication in J. Amer. Chem. Soc.

(181) See, among others, (a) W. Oroshnik and R. A. Mallory, J. Amer. Chem. Soc., 72, 4608 (1950); (b) E. Hamanaka, Ph. D. Thesis, Harvard University, Feb., 1967, pp 11-14; B. W. Erickson, Ph.D. Thesis, Harvard University, May, 1970, pp 90-96.

SCHEME II. Synthesis of 12-Hydroxy-4,8-dodecadienoic Acid Lactone



was prepared in high yield by cleavage of 2,5-dihydrofuran;¹⁸² selective displacement of tosylate was successfully accomplished with diethyl sodiomalonate.¹⁸³ After converting an acetate to a THP ether, the diester 54 was decarboethoxylated in one step by a recently reported method using sodium cyanide in DMSO.¹⁸⁴

From this point, dibromoester 50 was prepared by a series of standard reactions and cyclized in high yield by slow addition (motor-driven syringe) to an excess of nickel carbonyl in N-methylpyrrolidone under argon at 50°. Glpc analysis of the unsaturated lactone (51) isolated by tlc from the reaction mixture showed one major component and two minor components (90:4:6); by analogy with previous work¹⁶⁵ and from the product's infrared spectrum, which contained a strong absorption for trans CH=CH (970 cm⁻¹) and lacked one for cis CH=CH (690-715 cm⁻¹), the major component was formulated as the trans, trans isomer. The two minor isomers were not sufficiently separated from the major isomer to permit their isolation by either glpc or high-pressure liquid chromatography; consequently, the geometry about the double bonds of the

(182) M. H. Karger and Y. Mazur, J. Amer. Chem. Soc., 90, 3878 (1968); idem, J. Org. Chem., 36, 528 (1971).

(183) For potential alkylation by ester enolates and related anions, see (a) M. W. Rathke and A. Lindert, J. Amer. Chem. Soc., 93, 2318 (1971); (b) A. I. Meyers and D. L. Temple, Jr., ibid., 92, 6644 (1970); (c) S. Watanabe, K. Suga, T. Fujita, and K. Fujiyoshi, Israel J. Chem., 8, 731 (1970).

(184) A. P. Krapcho, G. A. Glynn, and B. J. Grenon, Tetrahedron Lett., 215 (1967).

minor isomers is uncertain. Hydrogenation of the mixture of isomers produced a single product, identical with the product formed from peracid oxidation of cyclododecanone.¹⁸⁵

¹⁸⁵ K. Kosswig, W. Stumpf, and W. Kirchhof, Ann. Chem., 681, 28 (1965).

4. Experimental Section

1-Tosyloxy-4-acetoxy-2-butene.¹⁸² Anhydrous p-toluene-sulfonic acid (24.5 g, 142 mmol) and acetyl chloride (40 ml) were gently refluxed for 5 hr; evaporation of excess acetyl chloride under reduced pressure left acetyl-p-toluenesulfonate (27.9 g, 92%). It was treated with 2,5-dihydrofuran (22 ml) in acetonitrile (35 ml) under reflux for 16 hr; following the published procedure, 33.4 g (90%) of 1-tosyloxy-4-acetoxy-2-butene was isolated: nmr δ 2.01 (s, 3, CH₃CO), 2.43 (s, 3, CH₃-phenyl), 4.57 (m, 4, CH₂O), 5.70 (m, 2, vinyl), 7.27, 7.41, 7.71, 7.85 (AB q, 4, aromatic).

Ethyl 2-Carboethoxy-6-acetoxy-4-hexenoate (52). Diethyl malonate (53 ml, 0.35 mol) was added to sodium hydride (9.9 g of 57% in mineral oil, freed of oil with pet.ether, 0.234 mol) in THF (300 ml) at 0°, stirred for 20 min, diluted with HMPA (200 ml) at 0°, and treated with 1-tosyloxy-4-acetoxy-2-butene (33.2 g, 0.117 mol) in THF (30 ml) at room temperature for two hours. The reaction was treated with water (200 ml) and sodium bicarbonate solution (100 ml) and the organic layer was drawn off; the aqueous layer was extracted with petroleum ether (200, 200, 100 ml), and the combined organic solutions were extracted twice with sodium bicarbonate solution and dried. Distillation of the crude product through a short fractionation column yielded diethyl malonate (24.2 g), bp 74-75° (8 mm). Distillation was continued through a short-path column, yielding an additional 8.3 g of diethyl

malonate, bp $<40^{\circ}$ (0.07 mm); the main fraction of product distilled at $121-124^{\circ}$ (0.07 mm), yielding 20.0 g (63%) of 52 as a pale yellow liquid: ¹⁸⁶ ir 1745 cm^{-1} (s, C=O); nmr δ 1.27 (t, 6, $J = 7\text{ Hz}$, CH_3 of C_2H_5), 2.05 (s, 3, CH_3CO), 2.71 (m, 2, CH_2CH), 3.40 (m, 1, CHCH_2), 4.20 (q, 4, $J = 7\text{ Hz}$, CH_2 of C_2H_5), 4.64 (m, 2, CH_2O), 5.62 (m, 2, vinyl); mass spectrum parent m/e 272; tlc R_f 0.53 (2:1 pet.ether-ether, 2 dev., vis. C).

Mol. wt. Calcd for $\text{C}_{13}\text{H}_{20}\text{O}_6$: 272.1260. Found: 272.1255 (high resolution mass spectrometry).

Ethyl 2-Carboethoxy-6-hydroxy-4-hexenoate (53). Ethyl 2-carboethoxy-6-acetoxy-2-butene (5.0 g, 18.4 mmol) was dissolved in ethanol (25 ml) and treated with potassium carbonate (253 mg, 1.84 mmol) at 75° for 2 hr, at which point starting material was no longer present (tlc analysis). The reaction was cooled and ethanol was evaporated under reduced pressure; the residual oil was dissolved in ether, extracted twice with saturated sodium chloride solution, and dried. 3.99 g (94%) of product was isolated, from which a pure sample was obtained by preparative tlc (ether): ir 3560 (m, OH), 1750 (sh) and 1740 cm^{-1} (s, C=O); nmr δ 1.27 (t, 6, $J = 7\text{ Hz}$, CH_3 of C_2H_5), 2.67 (m, 3, CH_2CH and OH), 3.42 (m,

(186) Dialkylated product (about 10%) was not distilled and was thus separated. In separate experiments, carried out on a 1.5 mmol scale, it was found that dialkylation increased with solvent changes in the order THF-HMPA $<$ THF-DMF $<$ THF-DMSO $<$ HMPA $<$ THF (nmr analysis).

1, $\underline{\text{CHCH}}_2$), 4.20 (q, 6, $J = 7$ Hz, CH_2 of C_2H_5 overlapping CH_2O), 5.67 (m, 2, vinyl); mass spectrum parent m/e 213 ($M - 17$); tlc R_f 0.52 (ether, vis. C).

Ethyl 2-Carboethoxy-6-(2'-tetrahydropyranyloxy)-4-hexenoate (54). The hydroxydiester (53) isolated above was dissolved in ether (30 ml) and dihydropyran (3.4 ml, 34.6 mmol), cooled to 0° , treated with *p*-toluenesulfonic acid monohydrate (50 mg), and stirred for 2 hr at room temperature, at which point no starting material remained (tlc analysis). The reaction was extracted with sodium bicarbonate solution and dried (sodium sulfate) to yield 5.48 g (100%) of 54, pure by tlc analysis. A sample was purified by preparative tlc¹⁸⁷ (2:1 pet.ether-ether, 2 dev.): ir 1750 (sh), 1740 cm^{-1} (s, C=O); nmr δ 1.27 (t, 6, $J = 7$ Hz, CH_3 of C_2H_5), 1.63 (broad m, 6, C_3H_6 of THP), 2.68 (m, 2, $\underline{\text{CH}}_2\text{CH}$), 3.27-3.95 (m, 3, $\underline{\text{CHCH}}_2$ and $\underline{\text{CH}}_2\text{O}$ of THP), 4.20 (q, 6, $J = 7$ Hz, CH_2 of C_2H_5 overlapping CH_2O), 4.60 (m, 1, O-CH-O of THP), 5.59 (m, 2, vinyl); mass spectrum parent m/e 213 ($M - \text{OTHP}$); tlc R_f 0.54 (2:1 pet.ether-ether, 2 dev., vis. C).

Ethyl 6-(2'-Tetrahydropyranyloxy)-4-hexenoate (55).

The diester 54 isolated above was heated with sodium cyanide (1.72 g, 35.0 mmol) in DMSO (40 ml) at 160° for 4 hr.¹⁸⁴ The reaction was cooled, poured into a mixture of water (25 ml) and sodium chloride solution (25 ml), and extracted with

(187) pH 8 buffered silica gel plates were used.

petroleum ether (100, 100, 50 ml); the combined petroleum ether extracts were dried (potassium carbonate), yielding 2.86 g (64%) of 55, pure by tlc analysis. A sample was purified by preparative tlc¹⁸⁷ (3:1 pet.ether-ether, 2 dev.): 1742 cm^{-1} (s, C=O); nmr (# 8) δ 1.27 (t, 6, $J = 7$ Hz, CH_3 of C_2H_5), 1.66 (m, 6, C_3H_6 of THP), 2.38 (m, 4, $\text{CH}_2\text{CH}_2\text{CO}$), 3.59 (m, 2, CH_2O of THP), 4.14 (q, 4, $J = 7$ Hz, CH_2 of C_2H_5 overlapping with CH_2O), 4.65 (m, 1, O-CH-O of THP), 5.60 (m, 2, vinyl); mass spectrum parent m/e 242; tlc R_f 0.46 (3:1 pet.ether-ether, 2 dev., vis. C).

Mol. wt. Calcd for $\text{C}_{13}\text{H}_{22}\text{O}_4$: 242.1518. Found: 242.1518 (high resolution mass spectrometry).

6-(2'-Tetrahydropyranyloxy)-4-hexenoic Acid (56).

Ester 55 (650 mg, 2.69 mmol) was stirred with 0.5 M sodium hydroxide (13 ml, 6.5 mmol) at room temperature for 4 hr; after extraction of insoluble material with a small amount of ether, the basic solution was acidified to pH 3.5 with saturated sodium dihydrogen phosphate solution and the product was extracted with ether (5 times) and dried (sodium sulfate). 560 mg (97%) of 56 was isolated, pure by nmr analysis: ir 3300-2650 (broad, COOH), 1733 (sh) and 1712 cm^{-1} (s, C=O); nmr δ 1.63 (broad m, 6, C_3H_6 of THP), 2.39 (m, 4, $\text{CH}_2\text{CH}_2\text{CO}$), 3.58 (m, 2, CH_2O of THP), 4.17 (m, 2, CH_2O), 4.63 (m, 1, O-CH-O of THP), 5.58 (m, 2, vinyl), 8.13 (s, 1, COOH); mass spectrum parent m/e 214; tlc R_f 0.24 (1:1 pet.ether-ether, 2 dev., vis. B).

Mol. wt. Calcd for $C_{11}H_{18}O_4$: 214.1205. Found: 214.1197 (high resolution mass spectrometry).

6-(2'-Tetrahydropyranyloxy)-4-hexen-1-ol (57). Ester 55 (650 mg, 2.69 mmol) in THF (1 ml) was slowly added to lithium aluminum hydride (2.2 ml of 2.45 M, 5.38 mmol) in THF (5 ml) and stirred for 2 hr at room temperature. The reaction was diluted with ether (50 ml), carefully quenched with 1 M sodium hydroxide, filtered through Celite 545, and dried (sodium sulfate). The crude product was purified by preparative tlc¹⁸⁷ (1:2 pet. ether-ether, 2 dev.) to give 376 mg (70%) of 57: ir 3350 cm^{-1} (broad, OH); nmr (# 9) δ 1.63 (broad m, 8, C_3H_6 of THP and CH_2CH_2OH), 2.15 (t, 2, $J = 6\text{ Hz}$, $CH_2-C=C$), 2.66 (s, 1, OH), 3.61 (t, 4, $J = 6\text{ Hz}$, CH_2OH overlapping CH_2O of THP), 4.16 (m, 2, CH_2O THP), 4.64 (m, 1, O-CH-O of THP), 5.60 (m, 2, vinyl); mass spectrum parent m/e 200; tlc R_f 0.57 (ether, vis. G).

Mol. wt. Calcd for $C_{11}H_{20}O_3$: 200.1412. Found: 200.1410 (high resolution mass spectrometry).

1-Iodo-6-(2'-tetrahydropyranyloxy)-4-hexene (58). Alcohol 57 (376 mg, 1.88 mmol) was treated with p-toluene-sulfonyl chloride (895 mg, 4.7 mmol) in pyridine (10 ml) at 0° for 12 hr; tlc analysis showed no starting material remained. The reaction was diluted with ether (50 ml), extracted twice with sodium bicarbonate solution, and evaporated under reduced pressure; the residual oil was redissolved in ether, extracted with sodium bicarbonate solution, and dried (sodium sulfate). The crude tosylate was dissolved in acetone (10 ml)

and treated with sodium iodide in acetone (10 ml of 10%) at room temperature for 30 min and at 50° for 1 hr. After evaporation of solvent under reduced pressure, the residue was dissolved in ether, extracted with sodium bicarbonate solution, and dried (sodium sulfate) to give 536 mg (92%) of 58: nmr δ 1.63 (broad m, 6, C₃H₆ of THP), 1.69-2.44 (m, 4, CH₂CH₂-C=C), 3.18 (t, 2, J = 6.5 Hz, CH₂I), 3.35-4.03 (m, 2, CH₂O of THP), 4.17 (m, 2, CH₂OTHP), 4.61 (m, 1, O-CH-O of THP), 5.57 (m, 2, vinyl); tlc R_f 0.41 (3:1 pet.ether-ether, vis. A).

6'-(2''-Tetrahydropyranyloxy)-4'-hexen-1'-yl 6-(2'-Tetrahydropyranyloxy)-4-hexenoate (59). Carboxylic acid 56 (346 mg, 1.61 mmol) in DMF (5 ml) was slowly added to sodium hydride (75 mg of 57% in mineral oil, freed of oil with pentane, 1.78 mmol) in DMF (15 ml) with cooling and then stirred for 30 min at room temperature. The mixture was treated with iodide 58 (500 mg, 1.61 mmol) in DMF (5 ml) and stirred for 1 hr at room temperature and for 1 hr at 70°; tlc analysis at this point showed no iodide remained. The reaction was cooled, treated with water (25 ml) and sodium bicarbonate solution (50 ml), and extracted with petroleum ether (5 x 50 ml); the combined petroleum ether solutions were extracted with sodium bicarbonate solution and dried (sodium sulfate). 10% of the total crude product (627 mg) was purified by preparative tlc¹⁸⁷ (2:1 pet.ether-ether, 2 dev.), yielding 41 mg (64%) of 59: ir 1739 cm⁻¹ (s, C=O);

nmr (# 10) δ 1.65 (broad m, 14, C_3H_6 of THP overlapping CH_2CH_2O), 2.11 (broad t, 2, $J = 6$ Hz, $CH_2CH_2CH_2O$), 2.38 (m, 4, CH_2CH_2CO), 3.4-3.9 (m, 4, CH_2O of THP), 4.12 (q, 6, $J = 6$ Hz, CH_2OCO overlapping CH_2OTHP), 4.61 (m, 2, O-CH-O of THP), 5.58 (m, 4, vinyl); mass spectrum parent m/e 396; tlc R_f 0.58 (1:1 pet.ether-ether, vis. B).

Mol. wt. Calcd for $C_{22}H_{36}O_6$: 396.2512. Found: 396.2498 (high resolution mass spectrometry).

6'-Hydroxy-4'-hexen-1'-yl 6-Hydroxy-4-hexenoate (60).

Bis-THP ether 59 (564 mg of crude product isolated above) was treated with p-toluenesulfonic acid monohydrate (100 mg) in methanol (20 ml) and THF (3 ml) at room temperature for 2 hr, at which point no starting material remained (tlc analysis). The reaction was made basic with sodium bicarbonate solution and evaporated to dryness under reduced pressure; ether and a minimal amount of sodium bicarbonate solution were added (product water-soluble), and the product was extracted with ether (3 times) and dried. The crude product was purified by preparative tlc (ether, 2 dev.) to give 194 mg of 60 (60% from 63, 94% for hydrolysis): ir (chloroform) 3390 (s, OH), 1724 cm^{-1} (s, C=O); nmr δ 1.70 (m, 2, CH_2CH_2OCO), 2.16 (m, 4, allylic CH_2), 2.38 (m, 2, CH_2CO), 3.32 (s, 2, OH), 3.61 (t, 2, $J = 6$ Hz, CH_2OCO), 4.08 (m, 4, CH_2OH), 5.57 (m, 4, vinyl); mass spectrum parent m/e 228; tlc R_f 0.26 (ether, vis. B).

6'-Bromo-4'-hexen-1'-yl 6-Bromo-4-hexenoate (50).

Diol 60 (97 mg, 0.425 mmol) in ether (2 ml) was treated with

phosphorus tribromide (41 μ l, 0.425 mmol) at 0° for 12 hr shielded from light.⁷⁵ The reaction was diluted with ether, extracted with sodium bicarbonate solution, and dried to yield 124 mg (83%) of 50: ir 1740 cm^{-1} (s, C=O); nmr (# 11) δ 1.74 (m, 2, $\text{CH}_2\text{CH}_2\text{O}$), 2.16 (t, 2, $J = 6$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 2.43 (m, 4, $\text{CH}_2\text{CH}_2\text{CO}$), 3.92-4.20 (m, 6, CH_2Br and CH_2O), 5.68 (m, 4, vinyl); mass spectrum parent m/e 352, 354, 356 (1:2:1); tlc R_f 0.39 (3:1 pet.ether-ether, vis. A).

Mol. wt. Calcd for $\text{C}_{12}\text{H}_{18}\text{Br}_2\text{O}_2$: 351.9675. Found: 351.9683 (high resolution mass spectrometry).

12-Hydroxy-4,8-Dodecadienoic Acid Lactone (51).

Dibromide 50 (119 mg, 0.336 mmol) in N-methylpyrrolidone (2 ml) was slowly added via motor-driven syringe over a 3.5 hr period to nickel carbonyl (0.26 ml, 2.02 mmol) in N-methylpyrrolidone (10 ml) at 50°; the initially yellow to yellow-orange solution became green in about one hour. After stirring for 4 hr at 50°, ether (5 ml) was added and distilled from the reaction mixture 3 times. The mixture was carefully treated with water (15 ml) and 3N hydrochloric acid (5 ml), and the product was extracted with petroleum ether (5 x 20 ml) and dried (sodium sulfate). The crude product was purified by preparative tlc (10:1 pet.ether-ether, 2 dev.) to yield 49 mg (76%) of lactone 51, possessing a camphor-like odor: ir 1733 (s, C=O), 970 cm^{-1} (s, trans-C=C); nmr (# 12) δ 1.79 (m, 2, $\text{CH}_2\text{CH}_2\text{O}$), 2.09 and 2.33 (broad m, 10, $\text{CH}_2\text{-C=C}$ and CH_2CO); 4.07 (t, 2, $J = 5$ Hz, CH_2O), 5.32 (m,

4, vinyl); mass spectrum parent m/e 194; tlc R_f 0.53 (10:1 pet. ether-ether, 2 dev., vis. B). Glpc analysis (column F, 200°) showed one major component (t_r 6.2 min, 90%) and two minor components (t_r 6.8 min, 4% and t_r 7.3 min, 6%).

Mol. wt. Calcd for $C_{12}H_{18}O_2$: 194.1307. Found: 194.1305 (high resolution mass spectrometry).

Unsuccessful attempts to isolate pure samples of the three isomers were made by preparative glpc (columns F and S, 200°) and high pressure liquid chromatography (6 ft, Porasil, 1:1 petroleum ether-methylene chloride).

12-Hydroxydodecanoic Acid Lactone (61). a. Hydrogenation of 51. Lactone 51 (11 mg) in ethanol (0.5 ml) containing about 0.5 mg of 5% palladium-on-charcoal was opened to hydrogen at atmospheric pressure, but no hydrogenation had occurred after 1 hr (glpc analysis). Additional catalyst (about 0.5 mg) was added; after 15 min, a number of new peaks were present on glpc analysis and after 30 min, only a single new peak was observed. The reaction was diluted with ether, filtered through Celite 545, and evaporated under reduced pressure to yield 11 mg (100%) of 61: ir 1733 cm^{-1} (s, C=O); nmr δ 1.35 (s) with smaller absorptions out to 1.74 (18, saturated CH_2), 2.25-2.44 (m, 2, CH_2 -CO), 4.14 (broad t, 2, $J = 5\text{ Hz}$, CH_2O); t_r 4.6 min (column F, 200°).

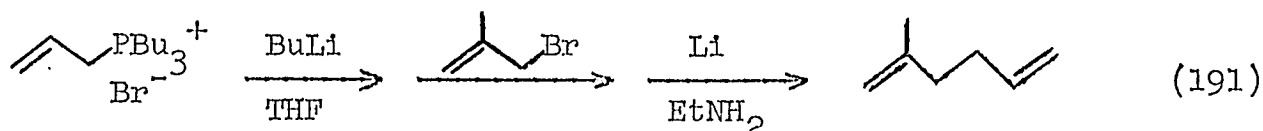
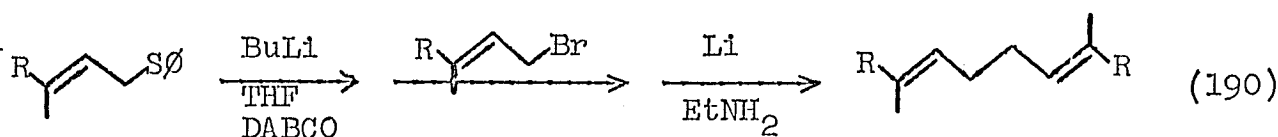
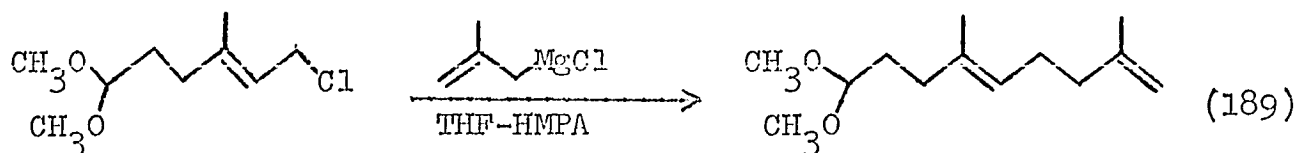
b. Baeyer-Villiger Oxidation of Cyclododecanone.¹⁸⁵ Cyclododecanone (10 g, 55 mmol) in glacial acetic acid (70 ml) was cooled to 10° and slowly treated with concentrated sulfuric acid (40 ml), keeping the temperature below 20°.

40% Peracetic acid in acetic acid (30 ml, 230 mmol) was then added at such a rate as to maintain the temperature at 23-30° with the aid of cooling. 15 min after addition was completed, the reaction was extracted with petroleum ether (4 x 200 ml); the combined petroleum ether solutions were extracted several times with 1 N sodium hydroxide, once with basic sodium thiosulfate solution and with water, and dried. The crude product was dissolved in ethanol (50 ml), treated with semicarbazide hydrochloride (5 g) and sodium acetate (8 g) on a steam bath for 10 min, cooled in ice, filtered, and extracted with petroleum ether 3 times; the petroleum ether solutions were extracted with sodium bicarbonate solution and dried. 3.0 g (28%) of 12-hydroxydodecanoic acid lactone was obtained, identical in all respects (ir, nmr, glpc, tlc) with the lactone obtained from hydrogenation (part a).

B. 1,5-Hexadienes from Allylic Sulfates.

1. Formation of 1,5-Hexadienes.

Current interest in acyclic polyisoprene compounds such as Cecropia juvenile hormone has focused considerable attention on the synthesis of 1,5-hexadienes, the structural unit characteristic of these isoprenoid molecules. A number of new procedures have been reported for selectively coupling dissimilar allylic groups by treating allylic nucleophiles with allylic halides; alkylations with lithio-1-trimethylsilylpropyne (see chapter one) represent a further example of this approach.¹⁸⁸

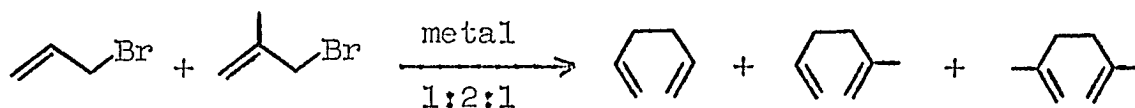


(188) For formation of 1,5-hexadienes by methods other than coupling of allylic groups, see (a) Claisen-Cope rearrangement: pp 66-67 of this thesis; (b) fragmentation of cyclic systems: J. A. Marshall and J. H. Babler, Tetrahedron Lett., 3861 (1970); J. A. Marshall, Synthesis, 229 (1971); R. Zurflüh, E. N. Wall, J. B. Siddall, and J. A. Edwards, J. Amer. Chem. Soc., 90, 6224 (1968); E. J. Corey and A. G. Hortmann, ibid., 87, 5736 (1965).

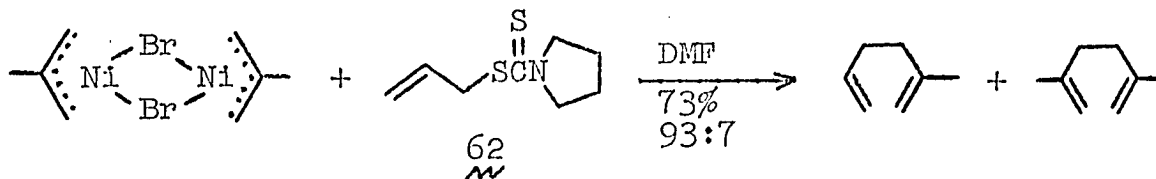
(189) G. Stork, P. A. Grieco, and M. Gregson, Tetrahedron Lett., 1393 (1969).

(190) J. F. Biellmann and J. B. Ducep, ibid., 3707 (1969).

Coupling of allylic halides by a host of metals is a well-known reaction;¹⁹² however, selective cross-coupling of two different halides is not possible and statistical mixtures of all three possible products are formed.^{192c,193} This lack



of selective cross-coupling has likewise been observed in coupling allylic alcohols with titanium complexes¹⁹⁴ and coupling allylic halides with trialkylboranes,¹⁹⁵ nickel carbonyl, and π -allyl nickel complexes.¹⁹⁶ In the latter case, though, a high degree of selective cross-coupling was achieved with allyl pyrrolidine dithiocarbamate (62).^{196b}



(191) E. H. Axelrod, G. M. Milne, and E. E. van Tamelen, J. Amer. Chem. Soc., 92, 2139 (1970); E. E. van Tamelen, P. McCurry, and U. Huber, Proc. Nat. Acad. Sci. U. S., 68, 1294 (1971).

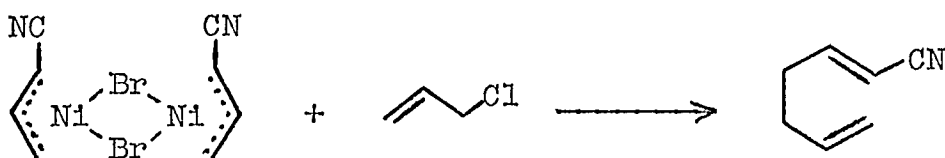
(192) (a) W. G. Young, J. F. Lane, A. Loshokoff, and S. Winstein, J. Amer. Chem. Soc., 59, 2441 (1937); (b) G. Dupont and G. Zuber, Bull. Soc. Chim. France, 342 (1959); (c) D. W. Hall and E. Hurley, Jr., Can. J. Chem., 47, 1238 (1969); (d) W. R. Dolbier, Jr., and C. A. Harmon, Chem. Commun., 150 (1971).

(193) A. L. Henne, H. Chanan, and A. Turk, J. Amer. Chem. Soc., 63, 3474 (1941); A. L. Henne and H. H. Chanan, ibid., 66, 392 (1944).

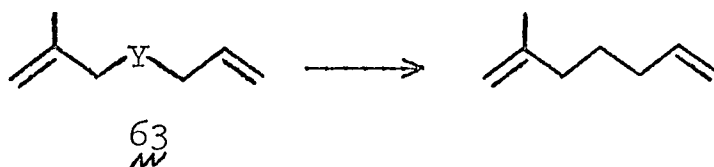
(194) E. E. van Tamelen and M. A. Schwartz, ibid., 87, 3277 (1965); K. B. Sharpless, R. P. Hanzlik, and E. E. van Tamelen, ibid., 90, 209 (1968); E. E. van Tamelen, B. Åkermark, and K. B. Sharpless, ibid., 91, 1552 (1969).

(195) A. Suzuki, S. Nozawa, M. Harada, M. Itoh, H. C. Brown, and M. M. Midland, ibid., 93, 1508 (1971).

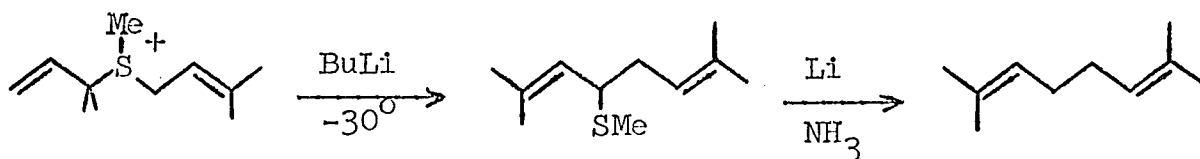
Allylic halides also show some degree of selectivity in coupling with π -allyl nickel complexes possessing an electro-negative substituent on the allyl ligand.¹⁹⁷



Selective cross-coupling can also be envisaged from the diallylic compound 63 by extrusion of the functional unit "Y";



the ease of ligand exchange in complexes where Y is a low-valent metal, however, has thus far hindered this approach. One example which has been reported is the rearrangement of diallylic sulfonium salts with subsequent cleavage of the alkylthio function.¹⁹⁸ In this section of chapter 3, a



second type of extrusion reaction is described, the reaction between diallylic sulfates and nickel carbonyl.

(196) (a) E. J. Corey, M. F. Semmelhack, and L. S. Hegedus, J. Amer. Chem. Soc., 90, 2416 (1968); (b) reference 156, pp 43-58; (c) reference 157, pp 1-19.

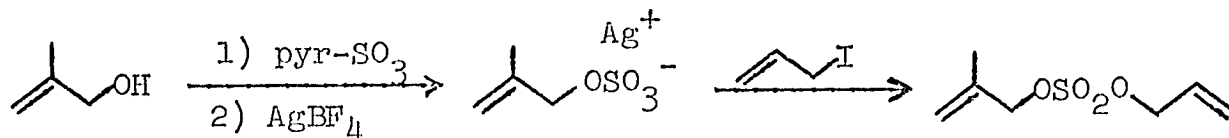
(197) G. P. Chiusoli, presented at XXIII International Congress of Pure and Applied Chemistry, Boston, 1971.

(198) J. E. Baldwin, R. E. Hackler, and D. P. Kelly, J. Amer. Chem. Soc., 90, 4758 (1968); G. M. Blackburn and W. D. Ollis, Chem. Commun., 1261 (1968).

2. Preparation of Diallylic Sulfates.

Diallyl and dimethallyl sulfate were prepared from the respective allylic halides and silver sulfate in an inert solvent. Although they were thermally unstable compounds which decomposed extensively if distilled,¹⁹⁹ purification was possible by chromatography; the impure sulfates also decomposed rapidly upon standing at room temperature.

Allyl methallyl sulfate was prepared from the readily available methallyl pyridinium sulfate;²⁰⁰ cationic exchange with silver tetrafluoroborate in acetone precipitated silver methallyl sulfate, which was alkylated with allyl iodide in cold ether. Cationic exchange using aqueous silver nitrate^{200a}



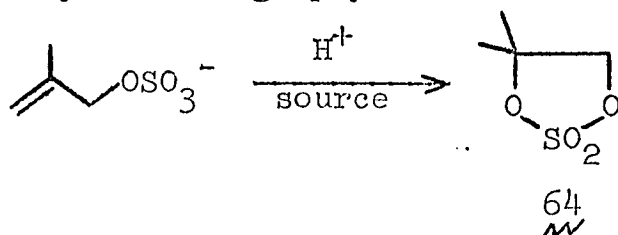
was prevented by the solubility of methallyl sulfate complexes in water; silver methallyl sulfate was also not precipitated from acetonitrile, while the insolubility of silver tetrafluoroborate in chloroform and of pyridinium methallyl sulfate in ether prevented use of these solvents.

Alkylation of silver methallyl sulfate was best conducted as a heterogeneous reaction in ether; much poorer results were obtained with acetone, acetonitrile, or THF as solvent. If the crude allyl methallyl sulfate was distilled, the

(199) Allyl iodide and silver sulfate are reported to give a liquid explosive on attempted distillation: J. von Braun and E. Müller, Chem. Ber., 50, 290 (1917).

(200) (a) A. E. Sobel and P. E. Spoerri, J. Amer. Chem. Soc., 63, 1259 (1941); (b) J. McKenna and J. K. Norymberski, J. Chem. Soc., 3889 (1957).

distillate contained a second product which was tentatively identified as $\underline{64}$, a cyclization product of an anionic methallyl sulfate; this by-product was not observed if purification was carried out by chromatography.



Although the three diallylic sulfates were too unstable for elemental analysis and gave no parent ion in their mass spectra, their spectra and chromatographic behavior leave no doubt of their identity. The infrared spectrum of allyl methallyl sulfate closely corresponded to that expected from superposition of the spectra of diallyl and dimethallyl sulfate. The chemical shifts of the methylene protons of the allylic sulfates are shown in table VIII and clearly reveal the expected deshielding effect of the sulfate moiety.

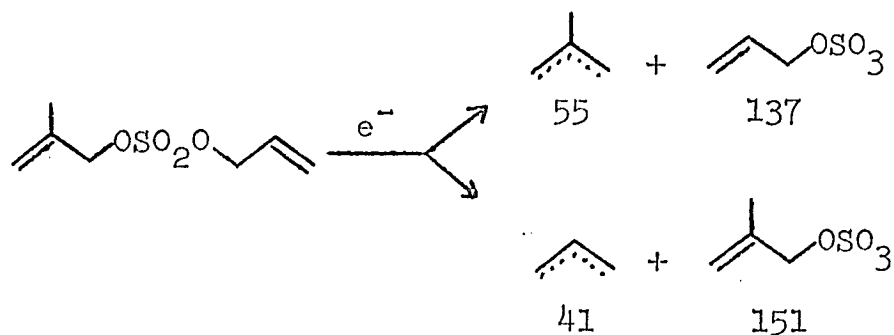
TABLE VIII. Chemical Shifts of Methyleneoxy Protons in Sulfate Derivatives of Allylic Alcohols

Compound	Chemical Shift ^a	
	(R = H)	(R = CH ₃) ^b
Methallyl alcohol		3.98
Pyridinium methallyl sulfate		4.47
Silver methallyl sulfate		4.54 ^c
Dimethallyl sulfate		4.65
Allyl alcohol	4.07	
Allyl iodide	4.52	
Pyridinium allyl sulfate	4.59	
Diallyl sulfate	4.73	
Allyl methallyl sulfate	4.74	4.65

^a Center of doublet, J = 5.5 Hz, expressed in δ units.

^b Singlet, expressed in δ units. ^c In D₂O.

The fragments of greatest m/e in the mass spectrum of allyl methallyl sulfate were 137 and 151 (about 1:1), expected to arise from C-O cleavage; the most abundant fragments had m/e values of 39, 41, and 55. This combined spectral data provides



good evidence for the formation of the three desired diallylic sulfates.

3. Reaction of Diallylic Sulfates with Nickel Carbonyl.

Diallyl sulfate was quantitatively converted to 1,5-hexadiene by nickel carbonyl in either DMF or tetraglyme at 0° within 1 hour; on the other hand, dimethallyl sulfate yielded only 20-30% of 2,5-dimethyl-1,5-hexadiene under the same conditions in DMF. Treatment of allyl methallyl sulfate with nickel carbonyl under a variety of conditions (see table IX) produced an unusual distribution of the three possible products (C₆, C₇, C₈) in an overall yield which varied from 20-50%; in each case, C₆ was the major component of the volatile products, C₇ was present to a lesser extent, and C₈ was a minor product if present at all. Furthermore, a similar

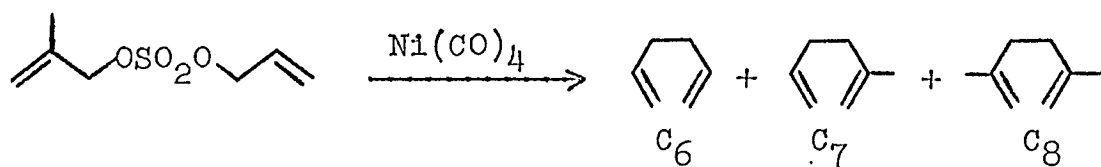
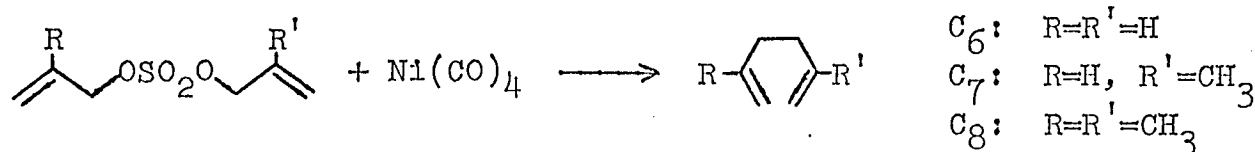


TABLE IX. Reaction of Diallylic Sulfates with Nickel Carbonyl.



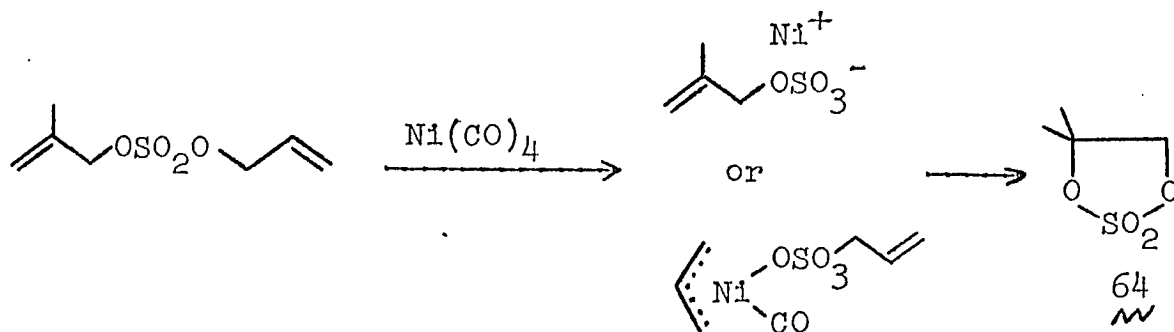
R	R'	Nickel Reagent	Solvent	Temp	Time	Yield of ^a			Distribution of ^a		
						C ₆ , C ₇ , C ₈	C ₆	C ₇	C ₈		
H	H	Ni(CO) ₄	DMF	0°	1 hr	100%	100				
"	"	"	TG	00°	30 min	99%	100				
CH ₃	CH ₃	"	DMF	0°	1 hr	23%				100	
"	"	"	"	"	"	29%				100	
CH ₃	H	"	"	r.t.	30 min	48%	64	26	10		
"	"	"	"	0°	1 hr	38%	66	31	3		
"	"	"	"	-10°	1 hr	23%	76	16	8		
"	"	"	TG	r.t.	15 min	40%	86	14	0		
"	"	"	"	"	1.5 hr	41%	80	20	0		
"	"	"	"	0°	1 hr						
"	"	"	"	r.t.	3 days	34%	95	5	0		
"	"	"	CH ₃ CN	r.t.	19 hr	36%	70	17	13		
"	"	"	HMPA	r.t.	20 hr		reaction incomplete ^b				
[H H] ^c		"	DMF	0°	1 hr	48%	52	29	19		
[CH ₃ CH ₃]											
CH ₃	H	none	"	r.t.	7 hr	0%					
"	"	(Ø ₃ P)Ni(CO) ₃ ^d	"	"	40 hr	22%	42	42	16		
"	"	"	TG	"	80 hr		reaction incomplete ^b				
"	"	Ni(COD) ₂ ^e	DMF	"	5 hr	40%	85	13	2		

^a Glpc analysis. ^b Reaction had not become green after the given length of time. ^c Mixture of diallyl and dimethallyl sulfates was used. ^d L. S. Meriwether and M. L. Fiene, *J. Amer. Chem. Soc.*, 81, 4200 (1959). ^e B. Bogdanović, M. Kröner, and G. Wilke, *Ann. Chem.*, 699, 1 (1966).

mixture was obtained if an equimolar combination of diallyl and dimethallyl sulfates was treated with nickel carbonyl, clearly indicating that exchange of allyl ligands occurred readily under these conditions in a manner analogous to that previously observed with allylic halides.¹⁹⁶

The infrared and nmr spectra of the distilled products confirmed glpc analysis that the only volatile compounds were C₆, C₇, and C₈; consequently, the low yield of coupling products is due to formation of a non-volatile by-product. Nickel allyl sulfate complexes which cannot couple the second allylic group are unlikely to be responsible since pyridinium allyl sulfate was converted to 1,5-hexadiene in 89% yield after one hour at room temperature in DMF; as anticipated, however, pyridinium methallyl sulfate gave only a 26% yield of C₈ (2 hr, room temperature) which was not increased by heating the reaction to 60°.

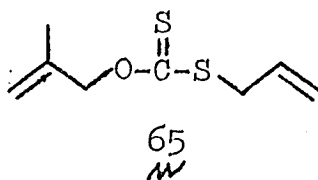
A more probable hypothesis, which also explains the selectivity between allyl and methallyl groups, is a Lewis-acid-catalyzed cyclization of a nickel methallyl sulfate intermediate, forming the previously observed cyclic sulfate (64); a nickel allyl sulfate complex is less likely to cyclize in such a manner since a secondary rather than tertiary



carbonium ion would be required. All attempts to isolate non-volatile products failed, however.

An interesting possibility for minimizing ligand exchange is slow addition of allyl methallyl sulfate to nickel carbonyl in DMF at 50° in a manner analogous to intramolecular cyclizations (see part A of this chapter); the very low concentration of allyl nickel complexes under these conditions might favor intramolecular coupling over ligand exchange or other side reactions.

It was also found that S-allyl O-methallyl dithiocarbonate (65) yielded no C₆, C₇, or C₈ when treated with nickel carbonyl at room temperature or 60° in DMF.



4. Experimental Section.

Diallyl Sulfate. A. In Ether. Allyl iodide (1.84 g, 10.9 mmol) and silver sulfate (2.37 g, 7.6 mmol) were stirred in anhydrous ether (30 ml) at 0° and shielded from light for 24 hr. Silver iodide was filtered and the filtrate was evaporated under reduced pressure (cold water bath); the crude product, which quickly darkened if warmed, was immediately dissolved in a small volume of chloroform and filtered through a short column of silica gel at 0°. ²⁰¹ 287 mg (29%) of diallyl sulfate was isolated as a colorless oil: ir 1393 and 1189 (s, SO₂ stretch), 979, 943, 916, 867 cm⁻¹ (all s); nmr δ 4.73 (d, 4, J = 5.5 Hz, CH₂O), 5.27-5.61 (m, 4, CH₂=C), 5.73-6.35 (m, 2, CH₂=CH).

b. In Acetonitrile. Allyl bromide (0.98 g, 8.08 mmol) and silver sulfate (1.26 g, 4.04 mmol) were stirred in acetonitrile (10 ml) at room temperature and shielded from light for 30 hr. The mixture was filtered, evaporated under reduced pressure, extracted with chloroform, filtered, and re-evaporated, leaving diallyl sulfate (227 mg, 31%) as a colorless oil, identical (ir, nmr) with the product obtained in part a.

Dimethallyl Sulfate. Methallyl bromide (1.35 g, 10.0 mmol) and silver sulfate (1.56 g, 5.00 mmol) were stirred in ether (150 ml) at 0° and shielded from light for 22 hr. The

(201) Davison 100-200 mesh silica gel and Fisher AR grade chloroform were used; decomposition of the product occurred on the column if the ethanol was removed from the chloroform.

product was isolated as described above, yielding 162 mg (16%) of dimethallyl sulfate after chromatography: ir 1395 and 1188 (s, SO₂ stretch), 920 cm⁻¹ (s); nmr δ 1.83 (d, 6, J = 1 Hz, CH₃), 4.65 (s, 4, CH₂O), 5.12 (m, 4, vinyl).

Pyridinium Methallyl Sulfate. Pyridine-sulfur trioxide complex (359 mg, 2.26 mmol) was suspended in chloroform²⁰² (2 ml) and treated with methallyl alcohol (0.115 ml, 2.26 mmol) at room temperature for 1 hr, forming a nearly complete solution. The mixture was filtered and evaporated to dryness, yielding pyridinium methallyl sulfate (quantitative) as a light yellow-brown oil which solidified upon continued evacuation with an oil pump: ir (chloroform) 3510-2130 (broad, NH), 1267, 1179, 1050, 1017, 990, 960, 910 cm⁻¹ (all s); nmr δ 1.72 (s, 3, CH₃), 4.47 (s, 2, CH₂O), 4.86 and 4.97 (two m, 2, vinyl).

Pyridinium Allyl Sulfate. Pyridinium allyl sulfate was prepared by the procedure described above, using allyl alcohol instead of methallyl alcohol: ir (chloroform) 3450-2550 (broad, NH), 1267, 1170, 910 cm⁻¹ (all s); nmr δ 4.59 (d of t, 2, J_d = 5.5 Hz, J_t = 1.2 Hz, CH₂O), 5.03-5.48 (m, 2, CH₂=C), 5.70-6.24 (m, 1, CH=CH₂).

Silver Methallyl Sulfate. Pyridinium methallyl sulfate (11.7 mmol) was prepared as described above, dissolved in acetone (3 ml), and added to silver tetrafluoroborate (2.28 g, 11.7 mmol) in acetone (17 ml) at room temperature. The

(202) Ethanol was removed by filtration through neutral Alumina I.

white precipitate was filtered, washed with a minimal amount of acetone, and dried over phosphorus pentoxide in vacuo, powdered, and redried to yield 2.87 g (95% over two steps) of silver methallyl sulfate: nmr (D_2O) δ 1.89 (s, 3, CH_3), 4.54 (s, 2, CH_2O), 5.12 (m, 2, vinyl). Volhard titration²⁰³ indicated the product contained 37.7% silver (90% of theoretical).

Allyl Methallyl Sulfate. Silver methallyl sulfate (2.62 g, 10.01 mmol) and allyl iodide (2.62 g, 15.6 mmol) were mechanically stirred in ether (100 ml) at 0° and shielded from light for 3 hr. The reaction was filtered and the filtrate was evaporated under reduced pressure ($0-5^\circ$ water bath) to give 1.85 g of a light orange oil which was dissolved in chloroform and filtered through silica gel at 0° .²⁰¹ 1.13 g (58%) of allyl methallyl sulfate was isolated: ir 1393 and 1190 cm^{-1} (s, SO_2 stretch); nmr (# 13) δ 1.82 (d, 3, $J = 1$ Hz, CH_3), 4.65 (s, 2, CH_2O of methallyl), 4.74 (d, 2, $J = 5.5$ Hz, CH_2O of allyl), 5.12 (m, 2, $CH_2=C$ of methallyl), 5.27-5.61 (m, 2, $CH_2=C$ of allyl), 5.72-6.25 (m, 1, $CH=CH_2$); mass spectrum parent m/e 151 (M - allyl) and 137 (M - methallyl).

b. By Distillation. Silver methallyl sulfate (1.02 g, 3.95 mmol) and allyl iodide (0.66 g, 3.95 mmol) were

(203) I. M. Kolthoff and E. B. Sandell, "Textbook of Quantitative Inorganic Analysis," 3rd ed., Macmillan Co., New York, 1952, p 545.

vigorously stirred in ether (30 ml) at 0° and shielded from light for 2.5 hr. The mixture was filtered and evaporated under reduced pressure and the crude product distilled bulb-to-bulb to give 126 mg (16%) of a colorless liquid; the nmr spectrum of the distillate was very similar to that of allyl methallyl sulfate, but contained two additional absorptions. Chromatography on silica gel²⁰¹ separated the second product: nmr δ 1.67 (s, 6, CH₃) and 4.43 (s, 2, CH₂); tlc R_f 0.37 (chloroform, vis. G) compared to R_f 0.70 for allyl methallyl sulfate.

Reactions of Allylic Sulfates with Nickel Carbonyl.

General Procedure. Nickel carbonyl (4 equiv) was added to solvent and brought to the desired reaction temperature (see table IX, p 129). The allylic sulfate was dissolved in a small volume of the appropriate solvent, cooled to the correct reaction temperature, and added to nickel carbonyl via syringe; carbon monoxide was evolved and the solution became orange or red. When the mixture had turned green, the reaction was considered complete; an internal glpc standard, either toluene or cyclohexane (better), was added and all volatile material was distilled in vacuo into a condenser cooled in liquid nitrogen. The yields of C₆, C₇ and C₈ given in table IX were determined by glpc analysis (columns B or N, 80°).

O-Methallyl S-Allyl Dithiocarbonate.²⁰⁴ A solution of

(204) B. Oddo and G. Del Rosso, Gazz. Chim. Ital., 391, 23 (1909). *mw*

potassium hydroxide (2.02 g, 36.0 mmol) and methallyl alcohol (15 ml) was diluted with acetone (20 ml) and treated with carbon disulfide (2.17 g, 36.0 mmol) at 0° for 10 min; allyl iodide (6.05 g, 36.0 mmol) was added, precipitating potassium iodide, and the mixture was stirred at room temperature for 2 hr. The mixture was diluted with ether, extracted with saturated sodium chloride solution, and dried. The crude product was dissolved in benzene and filtered through silica gel to yield allyl methallylxanthate as a yellow oil with a garlic odor: 1220 (m), 1180 (m), 1064 (s), 985 (m), 919 cm^{-1} (s); nmr δ 1.82 (s, 3, CH_3), 3.82 (d, 2, $J = 6.5$ Hz, CH_2S), 5.03 (s, 2, CH_2O), 5.06-6.27 (m, 5, vinyl).

Reaction of Allyl Methallylxanthate with Nickel Carbonyl.

a. At 25°. To DMF (20 ml) was added nickel carbonyl (1.4 ml, 10.7 mmol) and allyl methallylxanthate (504 mg, 2.68 mmol) in DMF (5 ml), forming a deep red mixture with gas evolution; after about 1 hr, a black precipitate formed. After 42 hr at room temperature, cyclohexane was added (50 μl), and 1,4-dibromo-2-butene (1.71 g, 8.0 mmol) in DMF (3 ml) was carefully added to decompose excess nickel carbonyl. The volatile products were distilled and analyzed by glpc as described above; no C_6 , C_7 , or C_8 was observed.

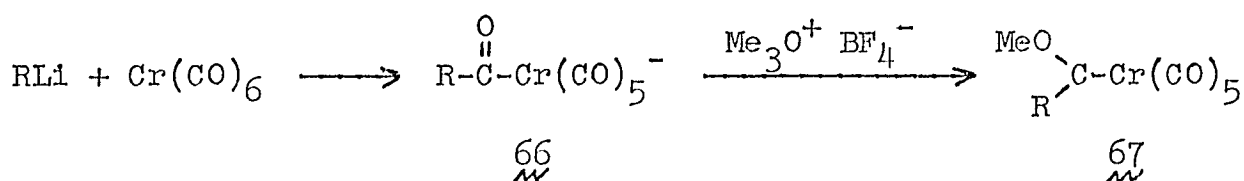
b. At 60°. The reaction was carried out as described above, except that the mixture was heated for 23 hr at 60° after addition of the reactants and the precipitate redissolved during this period. Glpc analysis again showed no C_6 , C_7 , or C_8 .

CHAPTER 4

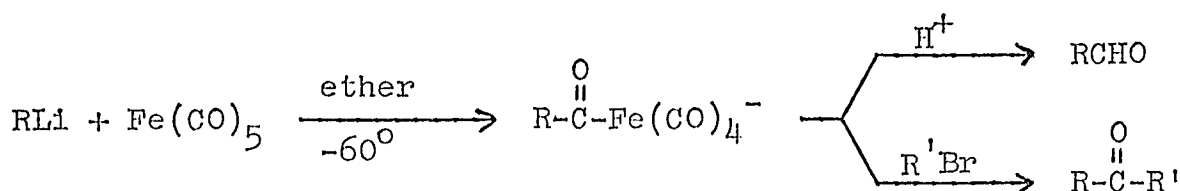
REACTIONS OF SULFUR- AND PHOSPHORUS-STABILIZED ANIONS WITH NICKEL CARBONYL AND α, β -UNSATURATED KETONES

A. Introduction.

Acylmetal complexes are generally formed when a metal carbonyl is treated with an alkyllithium or Grignard reagent. Chromium, molybdenum, and tungsten carbonyls yield relatively stable, isolable complexes (66) which can be converted to carbene complexes (67) by protonation or alkylation.²⁰⁵ The



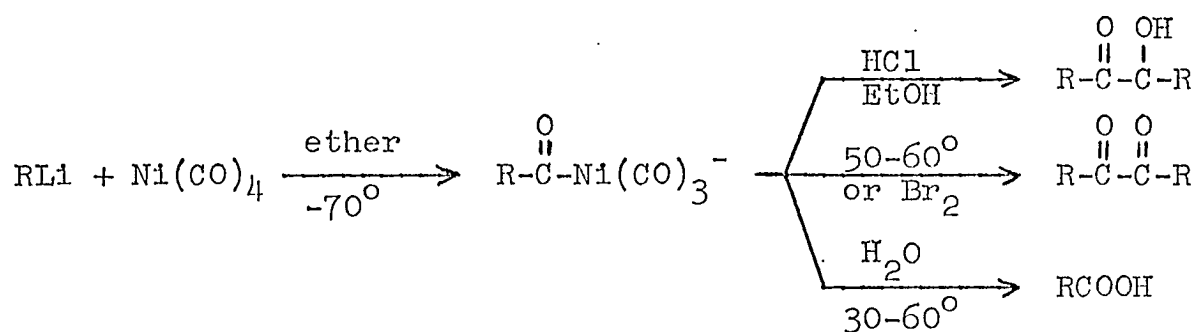
less stable acyliron complexes yield aldehydes on protonation and unsymmetrical ketones on alkylation,²⁰⁶ while the analogous acylnickel complexes yield a variety of carbonyl compounds, depending on the manner in which the intermediate is quenched.²⁰⁷ Lithium acetylides also react with metal



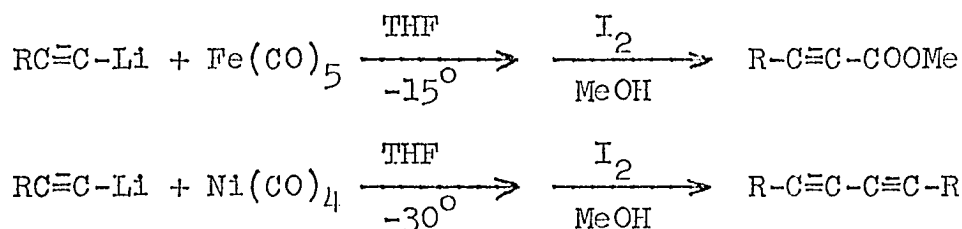
(205) E. O. Fischer and A. Maasböl, Chem. Ber., 100, 2445 (1967).

(206) M. Ryang, I. Rhee, and S. Tsutsumi, Bull. Chem. Soc. Japan, 37, 341 (1964); Y. Sawa, M. Ryang, and S. Tsutsumi, Tetrahedron Lett., 5189 (1969); E. O. Fischer and V. Kiener, J. Organometal. Chem., 23, 215 (1970).

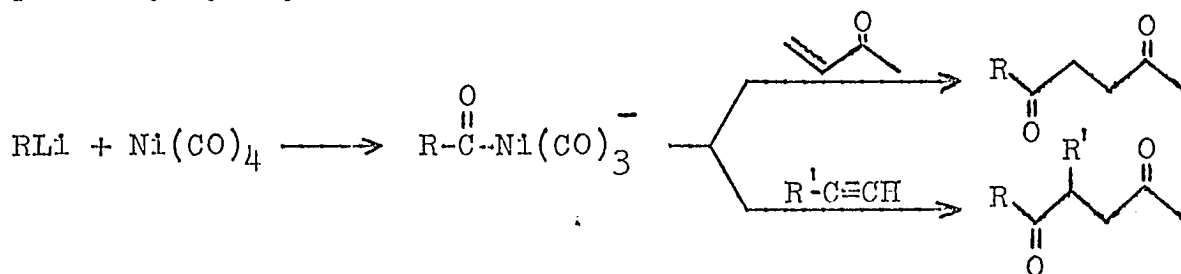
(207) S. Kwang-Myeong, Y. Sawa, M. Ryang, and S. Tsutsumi, Bull. Chem. Soc. Japan, 38, 330 (1965); *idem*, J. Organometal. Chem., 5, 305 (1966); F. L. Benton, M. C. Voss, and P. A. McCusker, J. Amer. Chem. Soc., 67, 82 (1945).



carbonyls, forming esters with iron carbonyl and coupling products without incorporation of carbon monoxide with nickel carbonyl.²⁰⁸



Anionic acylnickel complexes have recently been shown to add in a 1,4-manner to α,β -unsaturated carbonyl compounds.²⁰⁹ A closely related reaction has also been reported in which terminal acetylenes are directly converted to 1,4-diketones, possibly by way of unsaturated enone intermediates.²¹⁰

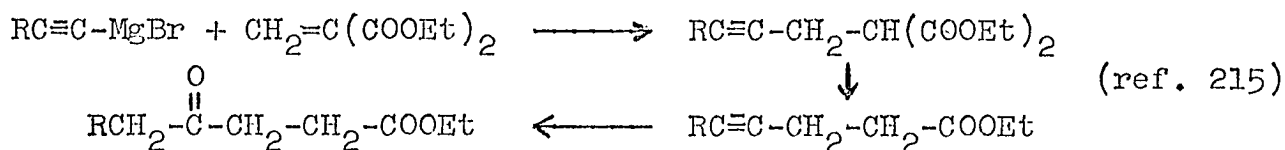
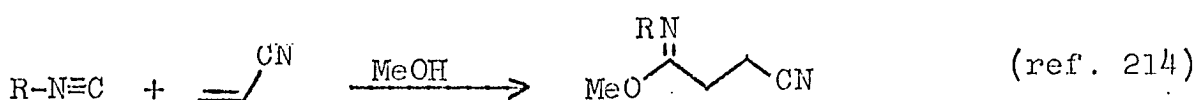
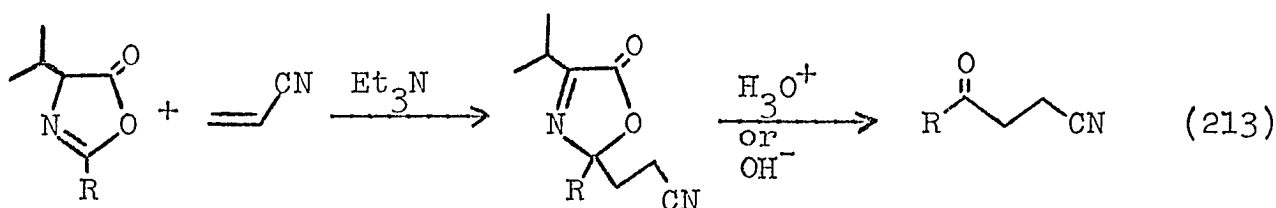
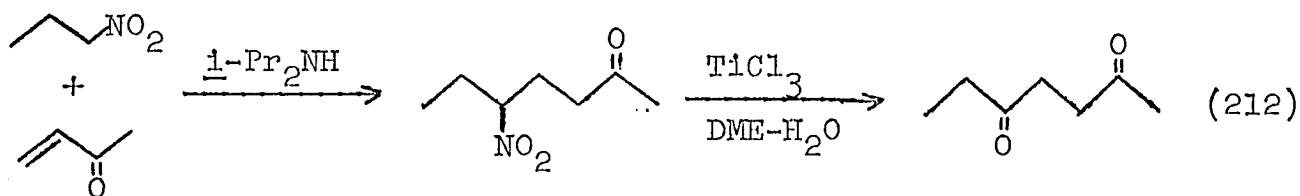


(208) I. Rhee, M. Ryang, and S. Tsutsumi, Tetrahedron Lett., 4593 (1969).

(209) E. J. Corey and L. S. Hegedus, J. Amer. Chem. Soc., 91, 4926 (1969); reference 157, chapter 4.

(210) Y. Sawa, I. Hashimoto, M. Ryang, and S. Tsutsumi, J. Org. Chem., 33, 2159 (1968).

1,4-Addition of acylnickel complexes represents the only known example of conjugate addition of acyl groups, although some masked acyl groups have been found which effect the same overall transformation.²¹¹



(211) 2-Lithio-1,3-dithiane does not undergo 1,4-addition: E. J. Corey and D. Crouse, *J. Org. Chem.*, **33**, 298 (1968). For general reviews of nucleophilic acyl moieties, see D. Seebach, *Angew. Chem. Int. Eng. Ed.*, **8**, 639 (1969); *idem*, *Synthesis*, **17** (1969); see also G. Stork and L. Maldonado, *J. Amer. Chem. Soc.*, **93**, 5286 (1971).

(212) J. E. McMurry and J. Melton, *J. Amer. Chem. Soc.*, **93**, 5309 (1971).

(213) W. Steglich, P. Gruler, G. Hofke, and W. König, *Angew. Chem.*, **83**, 725 and 727 (1971).

(214) T. Saegusa, Y. Ito, S. Tomita, H. Kinoshita, and N. Taka-ishi, *Tetrahedron*, **27**, 27 (1971).

(215) Y. Frangin, R. Couffignal, and M. Gaudemar, *Bull. Soc. Chim. France*, 246 (1971); see also H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **34**, 3615 (1969). For the conversion of γ,δ -acetylenic ketones to 1,4-diketones, see G. Stork and R. Borch, *J. Amer. Chem. Soc.*, **86**, 935 (1964).

In the previous work on 1,4-addition of acylnickel complexes, only simple alkylolithiums such as butyl, methyl, and phenyl had been employed;²⁰⁹ in this chapter, some attempts to extend the scope of this new reaction are reported, using certain organolithium reagents containing sulfur and phosphorus moieties.

B. Reaction of Anions with Nickel Carbonyl.

1. Anions from Methyl Sulfides and Mercaptans.

The anions investigated in this chapter were prepared by transmetallation, condensed with nickel carbonyl, and subsequently treated with benzalacetone, the most reactive unsaturated carbonyl compound reported in the initial work.²⁰⁹ A reaction temperature of -50° was generally employed and the organolithium reagent was stirred for two hours with nickel carbonyl before addition of benzalacetone; if benzalacetone was added much earlier, addition to the carbonyl group occurred without incorporation of carbon monoxide. Although diethyl ether was originally recommended as the better reaction solvent,²⁰⁹ THF was required to form homogeneous reactions in the present case.

Phenylthiomethylolithium (68) was readily prepared by metallation of phenyl methyl sulfide with sec-butyllithium in THF at -25° , a procedure superior to previous methods in that 68 is formed in high yield in the absence of tertiary amines.²¹⁶

(216) (a) E. J. Corey and D. Seebach, J. Org. Chem., 31, 4097 (1966); (b) H. Gilman and F. J. Webb, J. Amer. Chem. Soc., 71, 4062 (1949); (c) H. Gilman and W. J. Trepka, J. Organometal. Chem., 1, 222 (1964); (d) D. A. Shirley and B. J. Reeves, ibid., 16, 1 (1969).

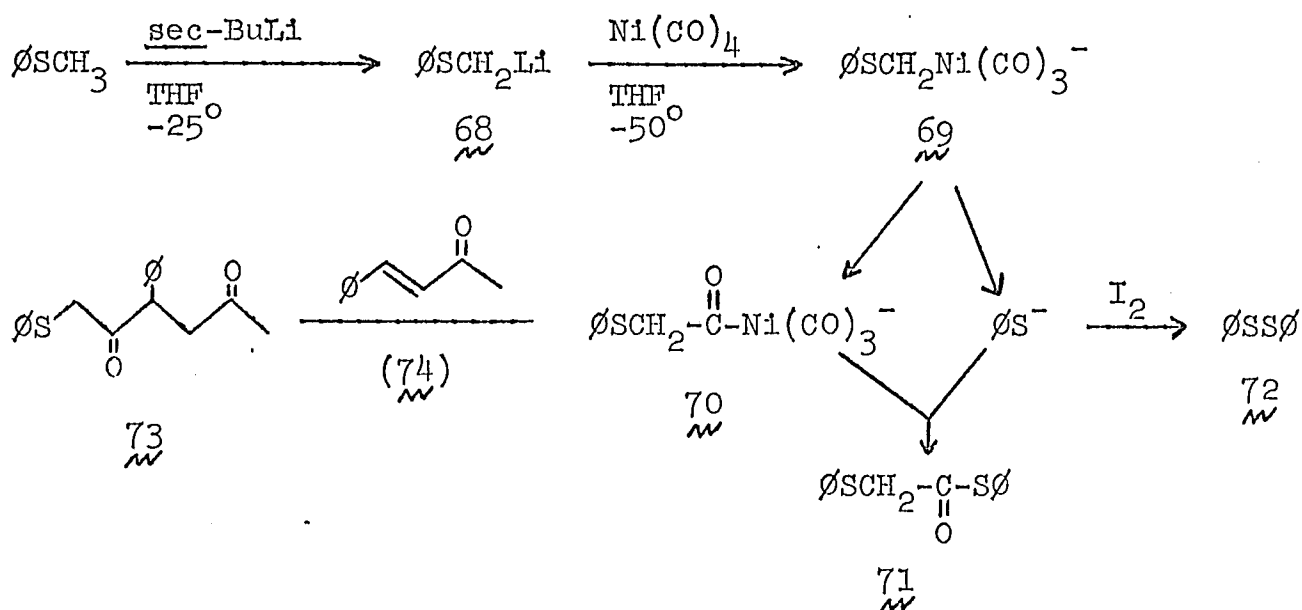


TABLE X. Reaction of Phenylthiomethyl lithium with Nickel Carbonyl and Benzalacetone

<u>68 + Ni(CO)₄</u>			<u>70 + 74</u>			Yield			
Mode of Addition	Time	Temp	Solvent	Time	Temp	71 ^a	72 ^a	73 ^b	74 ^b
Ni to Li	2 hr	-50°	THF	4 hr	-50°	22%	23%	31%	54%
Ni to Li	2 hr	-78°	"	4 hr	-78°	19%	-	34%	48%
Li(0°) to Ni	2 hr	-50°	THF-ether	10 hr	-50°	14%	31%	39%	36%
Li(-78°) to Ni	2 hr	-78°	"	18 hr	-78°	18%	41%	33%	36%
" "	30 min	"	"	20 hr	-78°	18%	39%	20%	35% ^c
Ni to Li	2 hr	-95°	THF	1 hr 20 hr	-95° -78°	17%	49%	30%	70%
warmed from frozen mixture	2 hr	-78°	"	25 hr	-78°	9%	63%	9%	68%

^a Yield based on phenyl methyl sulfide. ^b Yield based on benzalacetone (0.5 equiv). ^c 18% of 1,2-addition product also obtained.

Although stable in THF for several hours at -25° , phenylthio-methylolithium immediately began to decompose when treated with nickel carbonyl at -50° , forming the thiophenyl ester of phenylthioacetic acid (71), probably via attack of thiophenoxide on an acylnickel complex (70); the presence of thiophenoxide was also demonstrated by isolation of diphenyl disulfide after iodination of the reaction mixture.²¹⁷

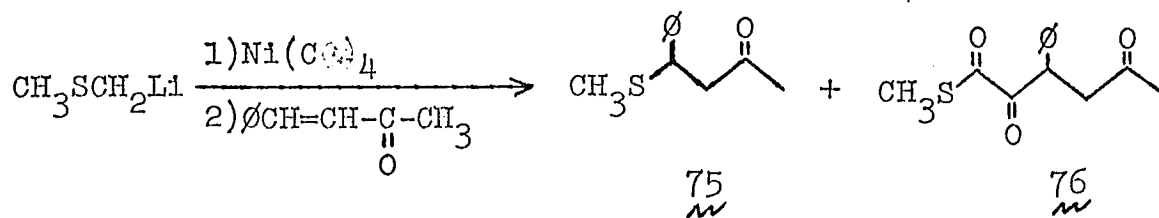
Thiolester (71) was observed by tlc analysis within 15 min. after addition of nickel carbonyl, a period of time less than that required for complete conversion of an alkylnickel complex (69) to an acylnickel complex (70). The acylnickel complex (70) did react with benzalacetone in the desired manner, producing a diketosulfide (73) in moderate yield. The relative distribution of products was generally insensitive to variations in reaction temperature, rate and mode of addition of the reagents, and solvent composition (see table X); no reaction conditions were found which suppressed this very facile α -elimination of thiophenoxide.

Somewhat different results were observed when methylthio-methylolithium, prepared by metallation of dimethyl sulfide with n-butyllithium and TMED in pentane,²¹⁸ was successively treated with nickel carbonyl and benzalacetone in ether.

α -Elimination again occurred, but the products isolated in this case were a β -ketosulfide (75) and a novel diketo-thiolester (76); the structure of the latter product was

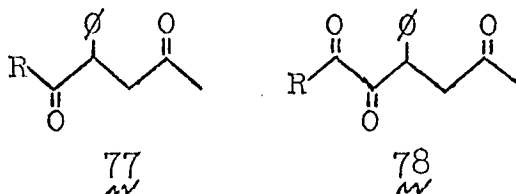
(217) Phenylthiomethylolithium does decompose to thiophenoxide under more vigorous conditions.^{216b}

(218) D. J. Peterson, J. Org. Chem., 32, 1717 (1967).



proposed on the basis of its infrared, nmr, and mass spectra. The nmr spectrum of 76 was similar to that of 73, but its infrared spectrum contained two carbonyl absorptions at 1724 and 1686 cm^{-1} and its mass spectrum indicated a molecular ion at m/e 250 with the composition $\text{C}_{13}\text{H}_{14}\text{O}_3\text{S}$, suggesting structure 76. Comparison of its nmr spectrum with those of similar compounds (see table XI) supported 76 as the structure of this unexpected product.

TABLE XI. Chemical Shifts of Some 2-Phenyl-1,4-diketones.

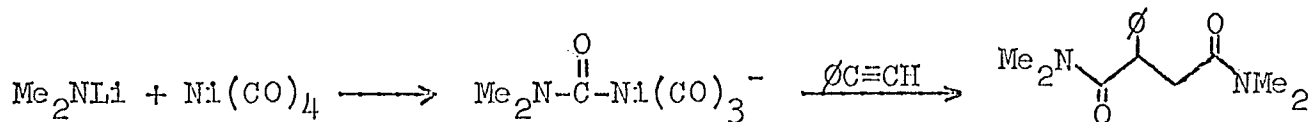


Compound	AMX System ^a		
	H _A	H _M	H _X
<u>77</u> , R = CH ₃ ^b	2.53	3.40	4.21
<u>77</u> , R = <u>t</u> -Bu ^b	2.51	3.41	4.60
<u>77</u> , R = CH ₂ S ϕ	2.61	3.43	4.47
<u>78</u> , R = <u>t</u> -Bu ^b	2.75	3.42	4.91
<u>76</u>	2.84	3.51	4.95

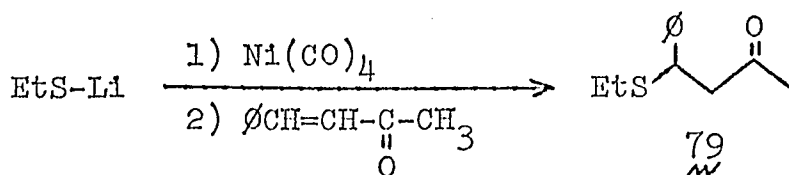
^a Center of absorption, expressed in δ units. ^b Values obtained from reference 200b.

Isolation of thiolester 76 prompted a study of lithium mercaptides with nickel carbonyl and enones as a general method for conjugate addition of either carboxyl or formyl groups, which are readily derived from thiolesters; conjugate addition by complexes of metal alkoxides or hydrides and nickel carbonyl has not yet been successful.²¹⁹

Recently, formamido-nickel complexes have been generated and added to acetylenes in the manner previously observed.²²⁰



Unfortunately, treatment of ethanethiol successively with butyllithium, nickel carbonyl, and benzalacetone at -50° simply yielded the Michael adduct of ethanethiol and benzalacetone (79) with no trace of material due to carbonyl insertion; at higher temperatures, extremely complex mixtures of products were obtained. The reactions were generally

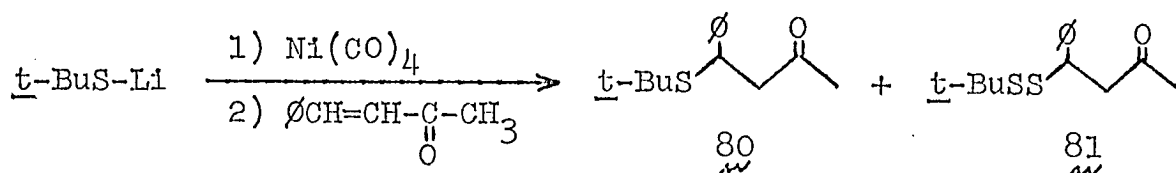


heterogeneous, except in THF above approximately -15° , at which point lithium thioethoxide reacted vigorously with nickel carbonyl, forming a yellow solution accompanied by evolution of carbon monoxide; however, the simple Michael adduct (79) was still the major product from benzalacetone.

(219) Unpublished work in these laboratories of L. S. Hegedus.

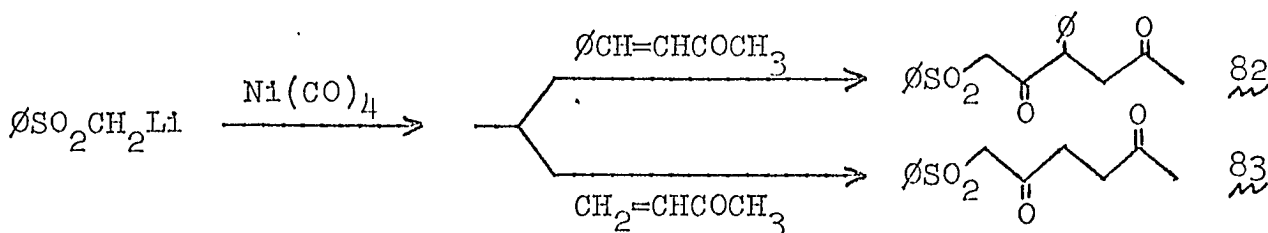
(220) S. Fukuoka, M. Ryang, and S. Tsutsumi, J. Org. Chem., 33, 2973 (1968); idem, ibid., 36, 2721 (1971).

Analogous reactions with t-butyl mercaptan, which formed soluble lithium and nickel complexes, likewise failed to yield any product with incorporation of carbon monoxide. However, cleavage of carbon-sulfur bonds was again observed, for a 1:1 mixture of a β -ketosulfide (80) and a β -ketodisulfide (81) was isolated.



2. From Methyl Sulfones and Sulfoxides.

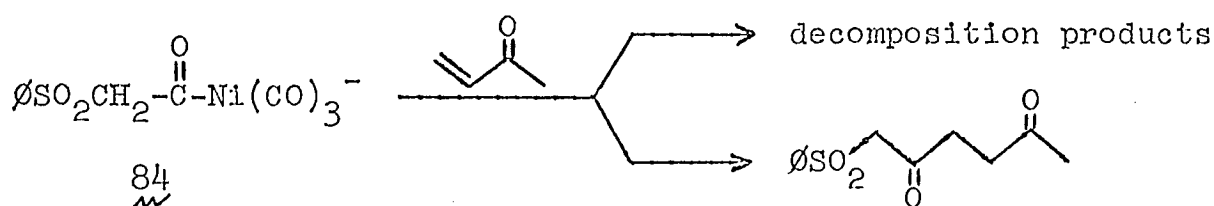
In the hope that higher oxidation states of sulfur would better stabilize anions against α -elimination, phenylsulfonylmethyl lithium was prepared and treated successively with nickel carbonyl and benzalacetone, forming the crystalline diketosulfone 82 in high yield with no significant by-products. Unfortunately, the analogous product 83 was obtained from 2-butenone only in low yield, and no products other than starting material were isolated from reactions with methyl cinnamate, methyl crotonate, or mesityl oxide.



Since the phenylsulfonylmethyl lithium-nickel carbonyl complex was insoluble in THF, analogous reactions were carried out with t-butyl methyl sulfone and dimethylsulfone, each of

which formed homogeneous solutions at all stages of the reaction. However, only starting material was isolated in the former case while an extremely complex mixture of products was obtained in the latter case. Furthermore, if the slurry of phenylsulfonylmethyl lithium and nickel carbonyl was mechanically stirred in a vigorous fashion instead of slowly stirred magnetically, a deep red homogeneous solution slowly formed which yielded no diketosulfone (82) upon addition of benzalacetone.

Thus, formation of 82 is apparently due to the insolubility of complex 84, which is stable as a precipitate, but unstable in solution; conjugate addition occurs only with very reactive enones which can successfully compete against decomposition of the nickel reagent. It is also possible that the enone

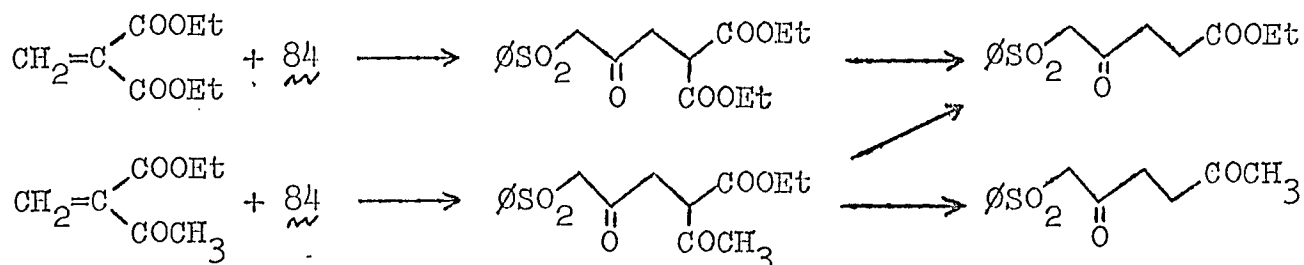


causes decomposition in some manner (e.g., electron-transfer and polymerization) since the nickel complex begins to dissolve upon addition of an unsaturated carbonyl compound which forms no 1,4-adduct.²²¹

One possible method to circumvent these difficulties is by use of methylenemalonic and methyleneacetoacetic esters,

(221) Methylene transfer from phenylsulfonylmethylsodium to various unsaturated compounds has been observed: Y. Yamamoto, T. Nisimura, and H. Nozaki, Bull. Chem. Soc. Japan, 44, 541 (1971).

which are very reactive toward 1,4-addition. Subsequent decarboethoxylation or deacetylation can be effected in a number of ways.²²²



Treatment of phenylsulfinylmethyl lithium with nickel carbonyl yielded nickel complexes unstable even at -78° , which decomposed before benzalacetone was added.²²³

3. From Phosphorus Compounds.

Dimethyl methyl phosphonate was readily metallated at -78° in THF,²²⁴ but addition of nickel carbonyl to this anion precipitated a dark red gum; none of the desired adduct with benzalacetone could be detected in the material isolated from the reaction. Analogous treatment of dimethyl methylphosphonothioate yielded a complex mixture of products. Addition of nickel carbonyl and benzalacetone to the anion derived from diphenyl methyl phosphine oxide also yielded a mixture of products; some 1,2-addition of the anion to

(222) (a) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., N. Y., 1965, pp 163-184; (b) A. P. Krapcho, G. A. Glynn, and B. J. Grenon, *Tetrahedron Lett.*, 215 (1967); (c) J. M. Lalancette and A. Lachance, *ibid.*, 3903 (1970); (d) Y. Kuo, F. Chen, C. Ainsworth, and J. J. Bloomfield, *Chem. Commun.*, 136 (1971).

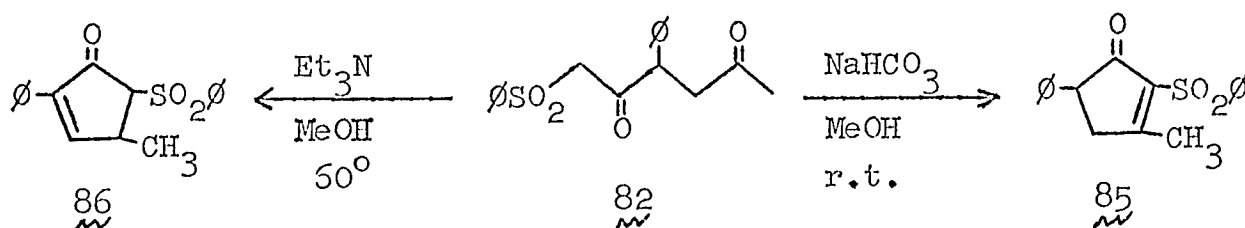
(223) Instability of arylsulfinylmethyl lithiums in ether solvents has been noted previously: J. Jacobus and K. Mislow, *J. Amer. Chem. Soc.*, 89, 5228 (1967).

(224) E. J. Corey and G. T. Kwiatkowski, *ibid.*, 88, 5654 (1966).

benzalacetone occurred at -78° , but no 1,4-adduct was found at -78° or -50° .

4. Formation of Cyclopentenones.

Cyclization of diketosulfone 82 to cyclopentenone 85 was readily accomplished with sodium bicarbonate in methanol at room temperature; under more vigorous conditions, using triethylamine in warm methanol, the more stable isomeric cyclopentenone 86 was formed.



Attempted cleavage of the phenylsulfonyl group from the ring using aluminum amalgam in aqueous THF at 0° ²²⁵ was slow and led to a complex mixture of products in each case.

86, (225) E. J. Corey and M. Chaykovsky, J. Amer. Chem. Soc., 86, 1539 (1964).

C. Experimental Section

The reactions described in this section were quenched in the following manner: saturated ammonium chloride solution was added at the reaction temperature and the mixture was allowed to warm to above 0°. Iodine in ether was carefully added via syringe until the iodine color was permanent for at least 15 min. The reaction was diluted with ether, extracted with saturated sodium chloride solution, saturated sodium sulfite solution, and again with saturated sodium chloride solution and dried over anhydrous magnesium sulfate.

1-Phenylthio-3-phenyl-2,5-hexanedione. Methyl phenyl sulfide (296 mg, 2.38 mmol) in THF (3 ml) was treated with sec-butyllithium (1.77 ml of 1.35 M, 2.38 mmol) at -25° for 30 min, yielding a light yellow-green solution from which a white solid precipitated during this period.²²⁶ The mixture was cooled to -50° and treated with nickel carbonyl (0.31 ml, 2.39 mmol), immediately forming an orange solution which slowly darkened to red. After 2 hr at -50° (Gilman test negative²²⁷), benzalacetone (175 mg, 1.20 mmol) in THF (0.5 ml) was added, producing a deeper red solution which was stirred at -50° for 4 hr. The crude dark oil isolated from the reaction (588 mg) was cleanly separated by preparative

(226) In a separate experiment, metallation was found to be 95% complete as determined by nmr analysis of the product isolated after quenching the reaction with excess trimethylchlorosilane.

(227) H. Gilman and F. Schulze, J. Amer. Chem. Soc., 47, 2002 (1925).

tlc (4:1 pet.ether-ether, 3 dev.) into four components, all of which were UV active. Recovered benzalacetone (54%) was identified by infrared, nmr, and tlc (R_f 0.53, 3:1 pet.ether-ether, 2 dev.) comparisons with an authentic sample. 110 mg (31%) of 1-phenylthio-3-phenyl-2,5-hexanedione was isolated and further purified by a second preparative tlc followed by bulb-to-bulb distillation at 150° (0.03 mm), yielding a waxy solid: mp 52-55°; ir 1724 cm^{-1} (s, C=O); nmr ($\#$ 14) δ 2.06 (s, 3, CH_3), 3.77 (s, 2, CH_2S), AMX system H_A 2.61, H_B 3.43, H_C 4.47 ($J_{AX} = 4.5$ Hz, $J_{MX} = 10$ Hz, $J_{AM} = 18$ Hz, 3, CH- CH_2), 7.11-7.26 (m, 10, phenyl); mass spectrum parent m/e 298; tlc R_f 0.41 (3:1 pet.ether-ether, 2 dev, vis. E).

Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{SO}_2$: C, 72.45; H, 6.08; S, 10.75. Found: C, 72.51; H, 6.14; S, 10.68.

The third component of the reaction mixture (69 mg, 22%) was identified as the thiophenyl ester of phenylthioacetic acid by comparison with an authentic sample prepared by known methods:²²⁸ mp 64-65° (from hexane twice with charcoal) [lit.^{228c} mp 64-65°]; ir 1725 (sh) and 1698 cm^{-1} (s, COSR); nmr δ 3.89 (s, 2, CH_2), 7.37 (m, 10, phenyl); mass spectrum parent m/e 260; tlc R_f 0.79 (3:1 pet.ether-ether, 2 dev.).

The final component of the reaction mixture was diphenyl

(228) (a) OSCH_2COOH : D. J. Pasto and R. Kent, J. Org. Chem., 30, 2684 (1965); (b) OSCH_2COCl : A. Mooradian, C. J. Cavallito, A. J. Bergman, E. J. Lawson, and C. M. Suter, J. Amer. Chem. Soc., 71, 3372 (1949); (c) $\text{OSCH}_2\text{COS}\phi$: L. Field and C. G. Carlile, J. Org. Chem., 26, 3170 (1961).

disulfide (60 mg, 46%): mp 60-61° (from hexane with charcoal) [lit.²²⁹ mp 61°]; ir 1577, 1475, 1440, 1027 and 687 cm⁻¹ (all s); nmr δ 7.20-7.62 (m, aromatic); tlc R_f 0.92 (3:1 pet.ether-ether, 2 dev.).

Methylthiomethyl lithium and Nickel Carbonyl. n-Butyllithium in pentane (2.88 ml of 1.18 M, 3.40 mmol) at 15° was treated successively with TMED (0.52 ml, 3.40 mmol), dimethyl sulfide (0.25 ml, 3.40 mmol), and n-undecane (0.13 ml, glpc internal standard), and the mixture was stirred at room temperature for 12 hr; an aliquot quenched with trimethylchlorosilane yielded 58% methyl trimethylsilylmethyl sulfide (glpc analysis, column G, 60°).²³⁰ The cloudy mixture of methylthiomethyl lithium was added dropwise to nickel carbonyl (0.44 ml, 3.40 mmol) in ether (4 ml) at -50°, forming a yellow-orange solution within a few minutes. After 2 hr at -50° (Gilman test negative²²⁷), benzalacetone (373 mg, 2.55 mmol) in ether (1 ml) was added, immediately producing a deep red solution which was stirred at -50° for 8 hr. The crude isolated product (587 mg) consisting of two immiscible oils was separated by preparative tlc (5:1 pet.ether-ether, 4 dev.) into three components. 21% of benzalacetone was recovered.

(229) Handbook of Chemistry and Physics, Chemical Rubber Co., 49th ed., 1968.

(230) If a 4 hr metallation period was used,²¹⁸ methyl trimethylsilylmethyl sulfide was formed in 80% yield, but some unreacted n-butyllithium remained so that 4-phenyl-2,5-nonanedione was found among the products of reaction with benzalacetone.

A small amount of 4-phenyl-4-methylthio-2-butanone (27 mg, 5%) was isolated and identified by comparison with the analogous ethyl and t-butyl compounds (see below): ir 1725 cm^{-1} (s, C=O); nmr δ 1.89 (s, 3, CH_3S), 2.09 (s, 3, CH_3CO), 3.00 (d, 2, $J = 8$ Hz, CH_2CO), 4.23 (t, 1, $J = 8$ Hz, CH-S), 7.30 (m, 5, phenyl); mass spectrum parent m/e 194; tlc R_f 0.57 (3:1 pet.ether-ether, 2 dev., vis. E).

The third component (87 mg, 13%) was identified as the thiomethyl ester of 3-phenyl-2,5-dioxohexanoic acid (76): ir 1724 (s, ketone C=O), 1686 cm^{-1} (s, -COSR); nmr δ 2.14 (s, 3, CH_3CO), 2.27 (s, 3, CH_3S), AMX pattern H_A 2.84, H_M 3.51, H_X 4.95 ($J_{AX} = 4.5$ Hz, $J_{MX} = 10.5$ Hz, $J_{AM} = 18$ Hz, 3, CH-CH_2), 7.26 (m, 5, phenyl); mass spectrum m/e (rel. intensity): 250 (M, 5), 218 (12), 175 (33), 147 (18), 131 (7), 119 (7), 117 (8), 104 (14), 103 (11), 77 (10), 43 (100); tlc R_f 0.41 (3:1 pet.ether-ether, 2 dev., vis. E). Two attempts were made to isolate an analytical sample by preparative glpc (column U, 210° and column R, 190°).

Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{O}_3\text{S}$: C, 62.37; H, 5.64; S, 12.81. Found: C, 64.56; H, 5.58; S, 8.65. C, 62.89; H, 5.61; S, 22.06. Mol. wt. Calcd for $\text{C}_{13}\text{H}_{14}\text{O}_3\text{S}$: 250.0664. Found: 250.0680. Calcd for $\text{C}_{13}\text{H}_{14}\text{OS}$: 218.0766. Found: 218.0758 (high resolution mass spectrometry).

Ethanethiol and Nickel Carbonyl. Ethanethiol (0.775 ml, 10.5 mmol) in ether (15 ml) was treated with n-butyllithium in pentane (8.50 ml of 1.18 M, 10.0 mmol) at 0° for 10 min

and with nickel carbonyl (1.30 ml, 10.0 mmol) at -50° for 6 hr; the resultant yellow slurry was treated with benzalacetone (1.46 g, 10.0 mmol) in ether (2 ml), producing an orange-brown slurry which was stirred at -50° for 6 hr. The crude product (2.39 g) was separated by preparative tlc (3:1 pet.ether-ether, 3 dev.) into three components. Small amounts of unreacted benzalacetone (9%) and 4-phenyl-2,5-nonanedione (from butyllithium, 4%) were isolated in addition to 4-phenyl-4-ethylthio-2-butanone (1.14 g, 55%), identified by comparison with an authentic sample prepared from ethanethiol and benzalacetone in the presence of piperidine:²³¹ ir 1721 cm^{-1} (s, C=O); nmr δ 1.12 (t, 3, $J = 7\text{ Hz}$, $\text{CH}_3\text{CH}_2\text{S}$), 2.05 (s, 3, CH_3CO), 2.31 (q, 2, $J = 7\text{ Hz}$, CH_2S), 2.94 (d, 2, $J = 7\text{ Hz}$, CH_2CO), 4.35 (t, 1, $J = 7\text{ Hz}$, CHS), 7.31 (m, 5, phenyl); mass spectrum parent m/e 208; tlc R_f 0.51 (4:1 pet.ether-ether, 2 dev.).

t-Butyl Mercaptan and Nickel Carbonyl. t-Butyl mercaptan (0.36 ml, 3.15 mmol) in ether (5 ml) was treated with n-butyllithium in pentane (2.55 ml of 1.18 M, 3.00 mmol) at 0° for 30 min, cooled to -50° , and treated with nickel carbonyl (0.39 ml, 3.00 mmol) for 3 hr. The resultant colorless solution was treated with benzalacetone (437 mg, 3.00 mmol) in ether (1 ml), forming a yellow solution which became colorless and deposited a white precipitate within 30 min; the mixture was stirred for 8 hr at -50° . The crude product

(231) R. B. Thompson, Ind. Eng. Chem., 43, 1638 (1951).

(774 mg) was separated by preparative tlc (3:1 pet.ether-ether, 2 dev) into recovered benzalacetone (57%) and 344 mg (approximately 43%) of a 1:1 mixture of two products which were separated by preparative tlc (methylene chloride, 2 dev.). 4-Phenyl-4-t-butylthio-2-butanone was identified by comparison with an authentic sample:²³¹ ir 1727 cm^{-1} (s, C=O); nmr δ 1.20 (s, 9, t-Bu), 2.04 (s, 3, CH_3CO), 2.88 (d, 2, $J = 7.5$ Hz, CH_2CO), 4.42 (t, 1, $J = 7.5$ Hz, CHS), 7.17-7.43 (m, 5, phenyl); tlc R_f 0.57 (methylene chloride, 2 dev., vis. E); glpc t_r 2.8 min (column J, 200°).

The second component of the 1:1 mixture was identified as 4-phenyl-4-t-butyldithio-2-butanone (81) which solidified on standing for a day: mp 58-60°; ir 1724 cm^{-1} (s, C=O); nmr δ 1.31 (s, 9, t-Bu), 2.06 (s, 3, CH_3CO), 3.05, 3.15, 3.20, 3.25 (2, CH_2CO), 4.30, 4.39, 4.44, 4.54 (1, CHS), 7.29 (s, 5, phenyl); mass spectrum parent m/e 268; tlc R_f 0.66 (methylene chloride, 2 dev., vis. E); glpc t_r 6.2 min (column J, 200°). An analytical sample was prepared by preparative glpc (column R, 200°).

Anal. Calcd for $\text{C}_{14}\text{H}_{20}\text{OS}_2$: C, 62.64; H, 7.51; S, 23.89. Found: C, 62.94; H, 7.50; S, 23.63. Mol. wt. Calcd for $\text{C}_{14}\text{H}_{20}\text{OS}_2$: 268.0954. Found: 268.0952 (high resolution mass spectrometry).

Phenylsulfonylmethyl lithium and Nickel Carbonyl. a. With Benzalacetone. Phenyl methyl sulfone (5.00 g, 32.1 mmol) in THF (80 ml) was treated with n-butyllithium in pentane (25.5 ml

of 1.26 M, 32.1 mmol) at -25° for 1 hr, forming a thick yellow slurry in 10-15 min; an aliquot quenched with trimethylchlorosilane indicated metallation was 79% complete (nmr analysis). The mixture was cooled to -50° and treated with nickel carbonyl (4.16 ml, 32.1 mmol), producing a less viscous yellow-orange slurry which was more easily stirred. After 2 hr at -50° , benzalacetone (2.34 g, 16.0 mmol) in THF (10 ml) was added, yielding a deep red solution which was stirred at -50° for 8 hr. All volatile material was completely removed from the crude product (8.0 g) by evaporation in vacuo. Trituration of the crude product with ether (about 100 ml) separated a tan solid which was filtered to yield 3.70 g of product, pure by tlc and nmr analysis; an additional 0.94 g of product was obtained from the filtrate (total 4.64 g, 88%). Two crystallizations from methanol yielded 1-phenylsulfonyl-3-phenyl-2,5-hexanedione as white crystals: mp $128-129.5^{\circ}$; ir (mull) 1715 (s, C=O), 1312, 1155 cm^{-1} (s, SO_2); nmr (# 15) δ 2.11 (s, 3, CH_3CO), AMX pattern H_A 2.59, H_M 3.33, H_X 4.46 ($J_{AX} = 4.5$ Hz, $J_{MX} = 9.5$ Hz, $J_{AM} = 18$ Hz, 3, CH- CH_2), 4.19 (d, 2, $J = 6$ Hz, CH_2SO_2), 7.00-7.98 (m, 10, phenyl); mass spectrum parent m/e 330; tlc R_f 0.35 (1:2 pet.ether-ether, 2 dev., vis. E). An analytical sample was prepared by crystallization from methanol and dried at 100° (0.03 mm) for 20 hr, mp $128-30^{\circ}$.

Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{O}_4\text{S}$: C, 65.43; H, 5.49; S, 9.71. Found: C, 65.49; H, 5.44; S, 9.69.

b. With 2-Butenone. The complex between phenylsulfonyl-methyl lithium and nickel carbonyl (3.21 mmol) in THF at -50° was prepared as described above and treated with freshly distilled 2-butenone (0.26 ml, 3.20 mmol) in THF (1 ml) at -50° for 8 hr. Separation of the crude product by preparative tlc (1:3 pet. ether-ether, 2 dev., then ether, 2.5 dev.) gave, in addition to recovered phenyl methyl sulfone (43%), 1-phenylsulfonyl-2,5-hexanedione (83) (71 mg, 9%): ir 1727 (s, C=O), 1325 and 1157 cm^{-1} (s, SO_2 stretch); nmr δ 2.15 (s, 3, CH_3CO), 2.83 (m, 4, CH_2CH_2), 4.28 (s, 2, CH_2SO_2), 7.55-8.03 (m, 5, phenyl); mass spectrum parent m/e 239 (M - 15); tlc R_f 0.43 (ether, 2 dev., vis. E). An analytical sample was prepared by preparative tlc (ether, 3 dev.) followed by bulb-to-bulb distillation at 100° (0.03 mm).

Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{SO}_4$: C, 56.67; H, 5.55; S, 12.61. Found: C, 56.92; H, 5.63; S, 12.35.

The preparative tlc separation also yielded more polar compounds whose spectra indicated they were higher-molecular-weight adducts of phenyl methyl sulfone and 2-butenone.

c. With Mesityl Oxide. Treatment of the phenylsulfonyl-methyl lithium-nickel carbonyl complex with mesityl oxide (0.5 equiv) slowly yielded a deep red solution in 4-5 hr; after 10 hr at -50° , the crude product consisted almost entirely of recovered phenyl methyl sulfone, identified by nmr and tlc analyses.

d. With Methyl Cinnamate. Addition of methyl cinnamate

(1 equiv) in a small volume of THF to the phenylsulfonylmethyl-lithium-nickel carbonyl complex at -50° in THF produced a red suspension in about 1 hr and a red solution in about 2 hr. After 8 hr at -50° , the crude product consisted only of the two starting materials, identified by nmr and tlc analyses.

e. With Methyl Crotonate. Treatment of the phenylsulfonylmethyl-lithium-nickel carbonyl complex with methyl crotonate (0.5 equiv) produced a deep red solution after several hours at -50° ; the reaction was stirred for 8 hr at -50° , stored for 12 hr at -78° , and stirred again for 6 hr at -50° . The crude product was principally phenyl methyl sulfone according to nmr and tlc analysis.

f. Using Mechanical Stirring. Phenylsulfonylmethyl-lithium (32.1 mmol) was prepared as described above in THF at -25° , using a mechanical stirrer fitted with a Teflon paddle;²³² an aliquot quenched with trimethylchlorosilane indicated metallation was 83% complete (nmr analysis). The mixture was cooled to -50° and treated with nickel carbonyl (4.16 ml, 32.1 mmol) in THF (10 ml), producing a transient yellow solution from which precipitated a bright yellow solid after less than one minute; upon vigorously stirring at -50° for 2 hr, the precipitate slowly redissolved to give a dark red solution. Benzalacetone (2.34 g, 16.0 mmol) in THF (10 ml)

(232) Nichrome wire was dissolved by the mixture containing nickel carbonyl.

was then added and the dark red solution was stirred at -50° for 8 hr. The dark red oil isolated from the reaction yielded no solid upon trituration with ether and tlc analysis indicated diketosulfone 82 was absent.

t-Butylsulfonylmethylolithium and Nickel Carbonyl.

t-Butyl methyl sulfone (160 mg, 1.18 mmol) in THF (5 ml) was treated with sec-butyllithium in cyclohexane (0.90 ml of 1.32 M, 1.18 mmol) at -30° for 30 min, yielding an opaque, pale yellow mixture; an aliquot quenched with trimethylchlorosilane indicated metallation was $>95\%$ complete (nmr analysis). The mixture was cooled to -50° , treated with nickel carbonyl (0.15 ml, 1.18 mmol) for 2 hr, and treated with benzalacetone (172 mg, 1.18 mmol) in THF (0.5 ml) for 8 hr at -50° . No compounds other than the two starting materials were found by tlc or nmr analysis of the crude product isolated from the reaction.

Methylsulfonylmethylolithium and Nickel Carbonyl.

Dimethylsulfone (381 mg, 4.05 mmol) in THF (15 ml) was treated with sec-butyllithium in cyclohexane (3.07 ml of 1.32 M, 4.05 mmol) at -25° for 30 min, yielding a white suspension; an aliquot quenched with trimethylchlorosilane indicated metallation was essentially complete (nmr analysis). The mixture was cooled to -50° and treated with nickel carbonyl (0.53 ml, 4.05 mmol) for 2 hr, slowly producing a red, nearly complete solution. Addition of benzalacetone (591 mg, 4.05 mmol) yielded a deep red solution within 5 min which was stirred at -50° for 8 hr. A very complex mixture was obtained

which was partially separated by preparative tlc (1:2 pet.ether-ether, 4 dev.) into seven components, most of which were still not pure compounds. Nmr analysis of various fractions and rechromatography of some of the fractions showed no evidence for the presence of the desired diketo-sulfone.

Phenylsulfinylmethyllithium and Nickel Carbonyl. Phenyl methyl sulfoxide (142 mg, 1.01 mmol) in THF (4 ml) was treated with methyllithium in ether (0.65 ml of 1.56 M, 1.01 mmol) at -78° for 15 min;²³³ the yellow solution was treated with nickel carbonyl (0.13 ml, 1.01 mmol) at -78° for 2 hr, yielding a red-orange solution. Addition of benzalacetone (148 mg, 1.01 mmol) in THF (0.5 ml) gave a red solution which was stirred at -78° for 11 hr. Separation of the crude product by preparative tlc (ether, 2 dev.) yielded benzalacetone (100% recovery) along with minor amounts of unidentified material.

Dimethyl Lithiomethylphosphonate and Nickel Carbonyl. Dimethyl methylphosphonate (513 mg, 4.14 mmol) in THF (5 ml) was treated with n-butyllithium in pentane (3.50 ml of 1.18 M, 4.14 mmol) at -78° for 15 min, immediately yielding a white precipitate.²²⁴ Dropwise addition of nickel carbonyl (0.54 ml, 4.14 mmol) in THF (1 ml) at -78° produced a red-orange solution which slowly darkened and precipitated a dark

(233) In a separate experiment, metallation was found to be essentially complete according to nmr analysis of the product obtained by quenching the reaction with D_2O .

red gum; after 2 hr, the mixture was treated with benzalacetone (302 mg, 2.07 mmol) in THF (0.5 ml) at -78° for 10 hr. Tlc and nmr analysis of the crude product (383 mg) indicated that it was predominantly recovered benzalacetone.

Similar results were obtained from reactions carried out at -50° or with a solvent mixture of THF and ether.

Dimethyl Lithiomethylphosphonothioate and Nickel Carbonyl.
Dimethyl methylphosphonothioate (244 mg, 1.74 mmol) in THF (5 ml) was treated with *n*-butyllithium in pentane (1.38 ml of 1.26 M, 1.74 mmol) at -78° for 10 min,^{224, 234} and then with nickel carbonyl (0.225 ml, 1.74 mmol) at -78° for 2 hr, slowly darkening from yellow to red (Gilman test negative²²⁷). Addition of benzalacetone (191 mg, 1.31 mmol) in ether (1 ml) yielded a deep red solution which was stirred at -78° for 8 hr. The crude viscous oil (405 mg) was separated by preparative tlc (4:1 pet.ether-ether, 3 dev.) into four principal components: dimethyl methylphosphonothioate (37%), benzalacetone (53%), 4-phenyl-2,5-nonanedione (from butyllithium, 9%) and 34 mg of a compound of unknown structure although the spectral data appear to exclude the desired diketophosphonothioate: ir 1720 (s, C=O), 1062, 1038, and 700 cm^{-1} (all s, may be associated with $-P(S)(OCH_3)_2?$); nmr

(234) In a separate experiment, metallation was complete within 5 min at -78° as determined by nmr analysis of the product isolated after quenching the reaction with excess trimethylchlorosilane. The metallation reaction was heterogeneous if ether was used instead of THF.

δ 2.15 (s, CH₃), 3.38-3.81 (t of q?) apparently overlapping a weaker absorption pattern partially observed on either side, 7.27 (m, phenyl); mass spectrum parent m/e 296; tlc R_f 0.21 (1:1 pet.ether-ether, 2 dev., vis. E). The material does appear to be an adduct of dimethyl methylphosphonothioate and benzalacetone although its exact structure is unknown; it is not the simple 1,2-addition product by comparison with an authentic sample.

A much more complex mixture of products was obtained if the reaction was carried out at -50°.

Diphenylphosphinoxymethyl lithium and Nickel Carbonyl.
Diphenyl methyl phosphine oxide (232 mg, 1.08 mmol) in THF (5 ml) was treated with methyllithium in ether (0.69 ml of a 1.56 M, 1.08 mmol) at 0° for 30 min, yielding a yellow solution. The solution was cooled to -78° and treated with nickel carbonyl (0.14 ml, 1.08 mmol); after 2 hr, the red solution was treated with benzalacetone (157 mg, 1.08 mmol) in THF (0.5 ml) at -78° for 21 hr. The crude product (326 mg) was separated by preparative tlc (ether, 2 dev.) into benzalacetone (65%), diphenyl methyl phosphine oxide (36%), and the product of 1,2-addition, 1-diphenylphosphinoxy-2-methyl-4-phenyl-3-buten-2-ol (74 mg, 19%), along with small amounts of unidentified material.

The same result was obtained using ether as solvent at -78°. At -50°, only starting materials were recovered from the reaction.

2-Phenylsulfonyl-3-methyl-5-phenyl-2-cyclopentenone (85).
1-Phenylsulfonyl-3-phenyl-2,5-hexanedione (516 mg, 1.56 mmol) was treated with sodium bicarbonate (131 mg, 1.56 mmol) in methanol (20 ml) for 1 hr at room temperature, yielding a yellow solution in 30-45 min and reprecipitating a white solid in about 50 min. The mixture was diluted with ether, extracted with saturated sodium chloride solution, and dried. The crude white solid (502 mg, 103%) was crystallized from methanol to give 407 mg (84%) of 2-phenylsulfonyl-3-methyl-5-phenyl-2-cyclopentenone as pale yellow needles: mp 138-143°; ir (Kaydol mull) 1724 (s, C=O), 1600 (s, C=C), 1305 and 1152 cm⁻¹ (s, SO₂); nmr (# 16) δ 2.70 (s, 3, CH₃), 2.90-3.68 (m, 3, CH-CH₂), 6.89-8.14 (m, 10, phenyl); mass spectrum parent m/e 312; tlc R_f 0.44 (1:2 pet.ether-ether, 2 dev., vis. A). An analytical sample was prepared by four crystallizations from methanol and dried at 100° (0.02 mm) overnight.

Anal. Calcd for C₁₈H₁₆O₃S: C, 69.20; H, 5.16; S, 10.27. Found: C, 69.36; H, 5.14; S, 10.24.

2-Phenyl-4-methyl-5-phenylsulfonyl-2-cyclopentenone (86). 1-Phenylsulfonyl-3-phenyl-2,5-hexanedione (501 mg, 1.52 mmol) was treated with triethylamine (0.21 ml, 1.52 mmol) in methanol (20 ml) at room temperature for 45 min, yielding a yellow solution which was heated at 55° for 2 hr; tlc analysis after 1 hr of heating indicated both isomeric cyclopentenones 85 and 86 were present. The reaction was

diluted with ether, extracted with sodium chloride solution containing 0.1N hydrochloric acid, and dried. The yellow oil isolated from the reaction was purified by preparative tlc (1:1 pet.ether-ether, 2 dev., then 1:2 pet.ether-ether, 2 dev.) to yield 194 mg (41%) of a viscous oil which was crystallized from methanol, yielding white crystals of 2-phenyl-4-methyl-5-phenylsulfonyl-2-cyclopentenone: mp 113-114°; ir (Kaydol mull) 1712 (s, C=O), 1622 (w, C=C), 1302 and 1143 cm^{-1} (s, SO_2); nmr (# 17) δ 1.39 (d, 3, $J = 7$ Hz, CH_3), 3.43-3.80 (m, 2, CHCH), 7.28-8.05 (m, 11, phenyl and vinyl); mass spectrum parent m/e 312; tlc R_f 0.60 (1:2 pet.ether-ether, 2 dev.). A sample was dried at 100° (0.02 mm) overnight and submitted for analysis.

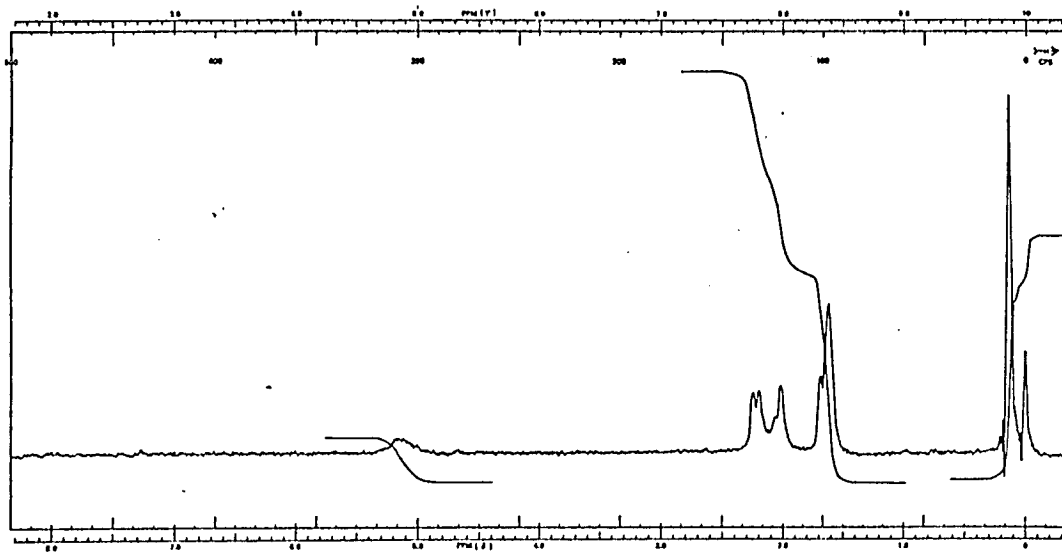
Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{O}_3\text{S}$: C, 69.20; H, 5.16; S, 10.27.
Found: C, 69.40; H, 5.20; S, 10.26.

Attempted Cleavage of Phenylsulfonyl Groups. a. From 85.

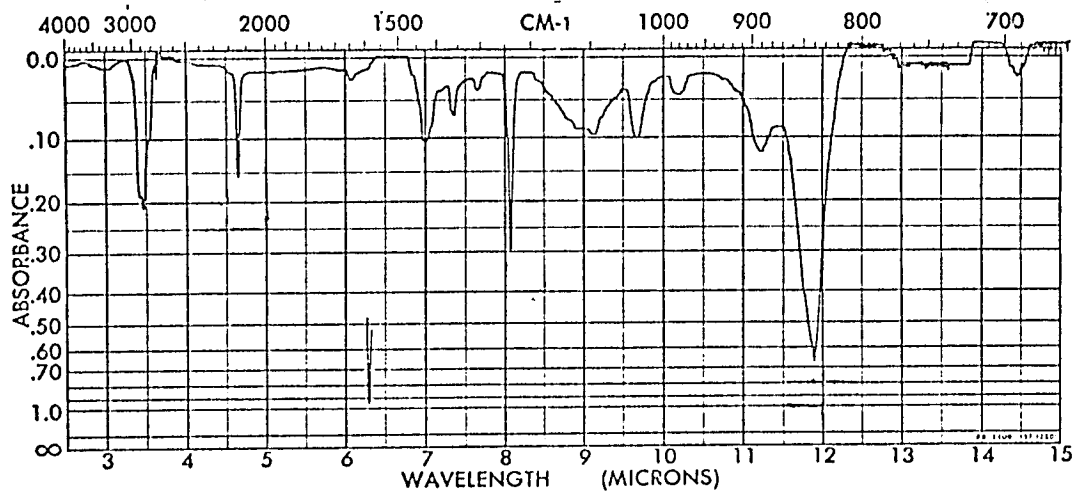
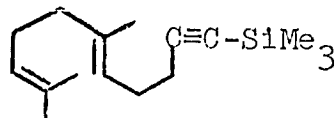
2-Phenylsulfonyl-3-methyl-5-phenyl-2-cyclopentenone (85) (75 mg, 0.24 mmol) was treated with aluminum amalgam (65 mg Al foil, 2.4 mmol) in THF (3 ml) and water (0.3 ml) at 0°;²²⁵ starting material was still present after 30 min, but absent after 1 hr, according to tlc analysis, which showed only a streak with no distinct products visible. The reaction was diluted with ether, extracted with 3N hydrochloric acid, and dried, yielding 98 mg of a complex mixture of products (tlc and nmr analysis).

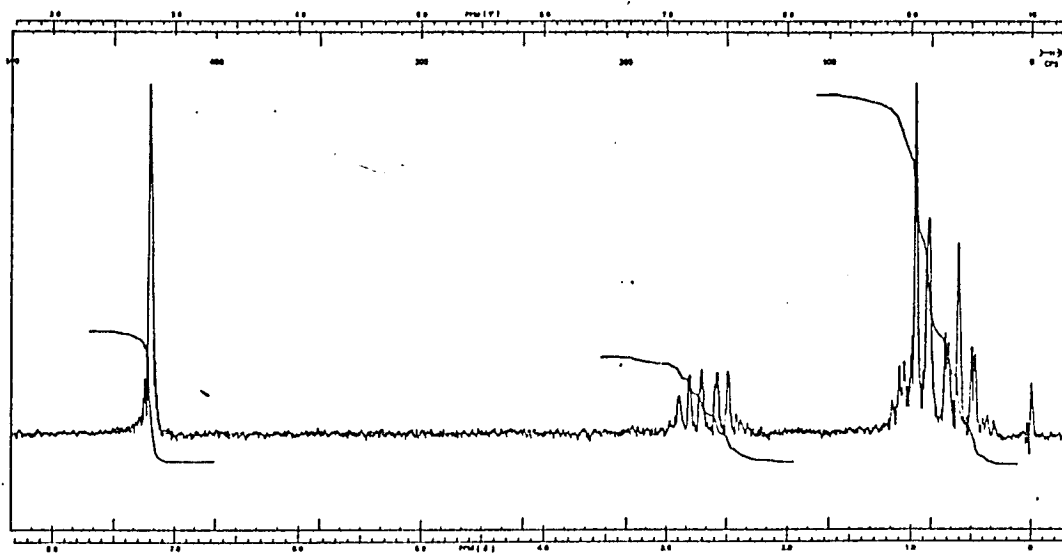
b. From 86. 2-Phenyl-4-methyl-5-phenylsulfonyl-2-cyclo-

pentenone (86) (13 mg, 0.042 mmol) was treated with aluminum amalgam (11 mg Al foil, 0.42 mmol) in THF (1 ml) and water (0.1 ml) at 0°; ²²⁵ tlc analysis showed starting material required 75 min for complete consumption and a second, less polar product slowly formed. The reaction was diluted with ether, extracted with 1N hydrochloric acid, dried, and separated by preparative tlc (1:1 pet.ether-ether), yielding 3 mg of the new product; its nmr, infrared, and mass spectra indicated a mixture of compounds which did not contain 2-phenyl-4-methyl-2-cyclopentenone.

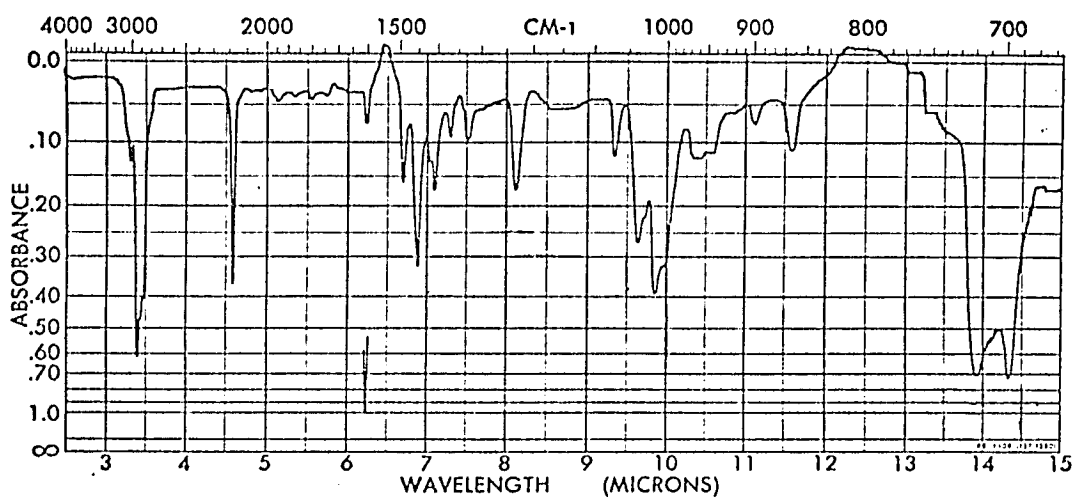
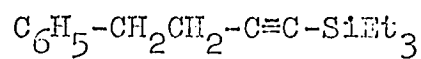


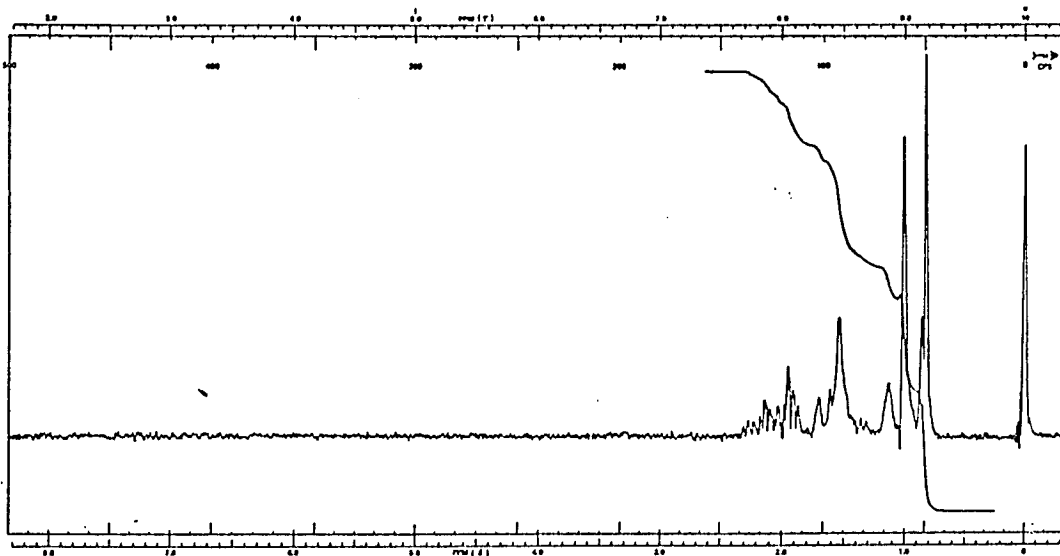
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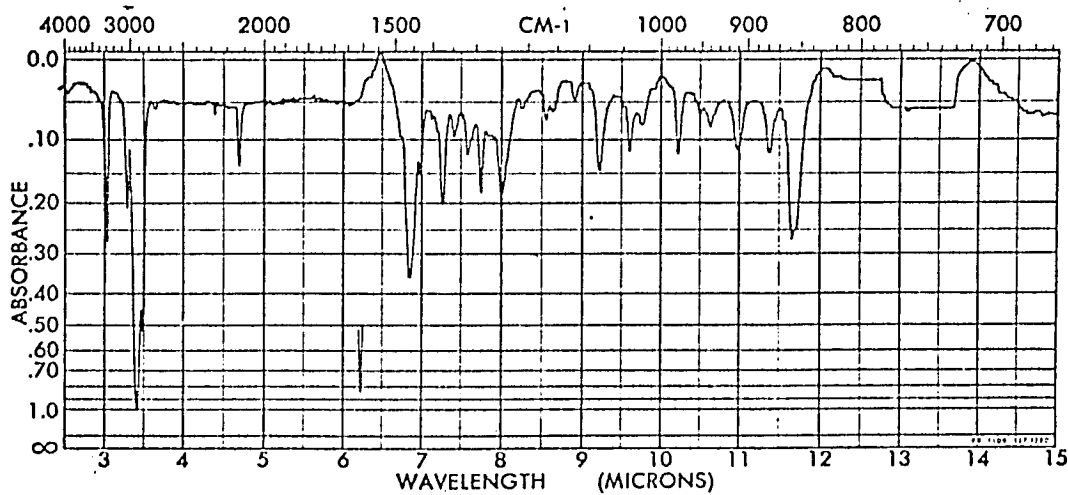
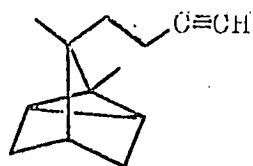


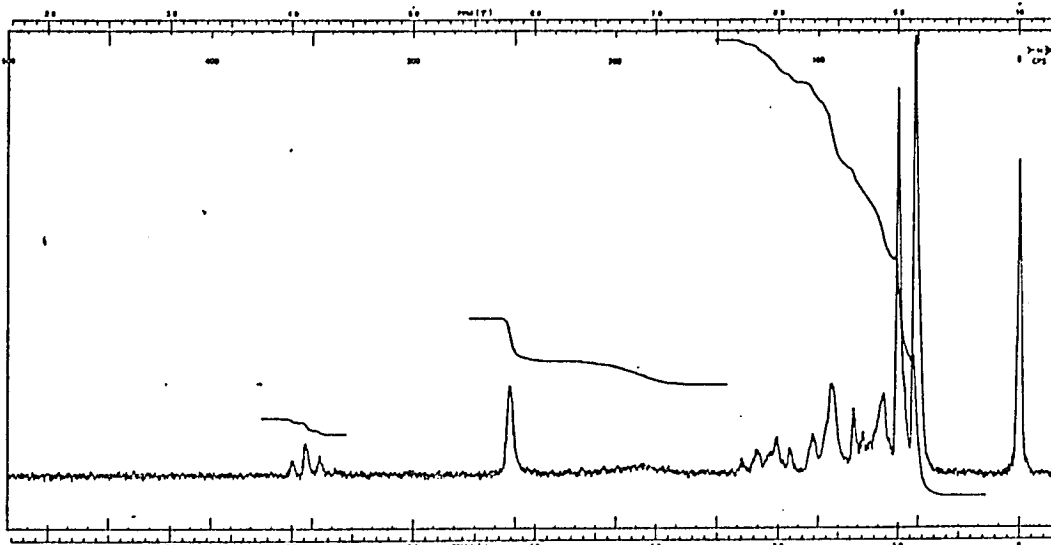
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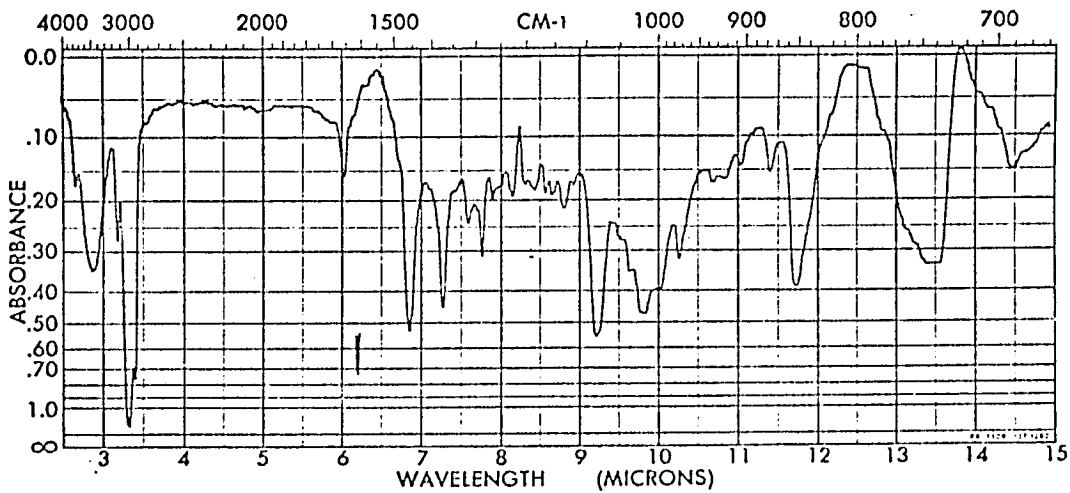
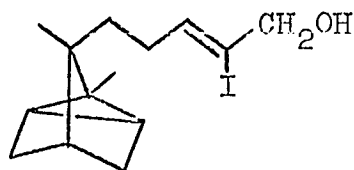


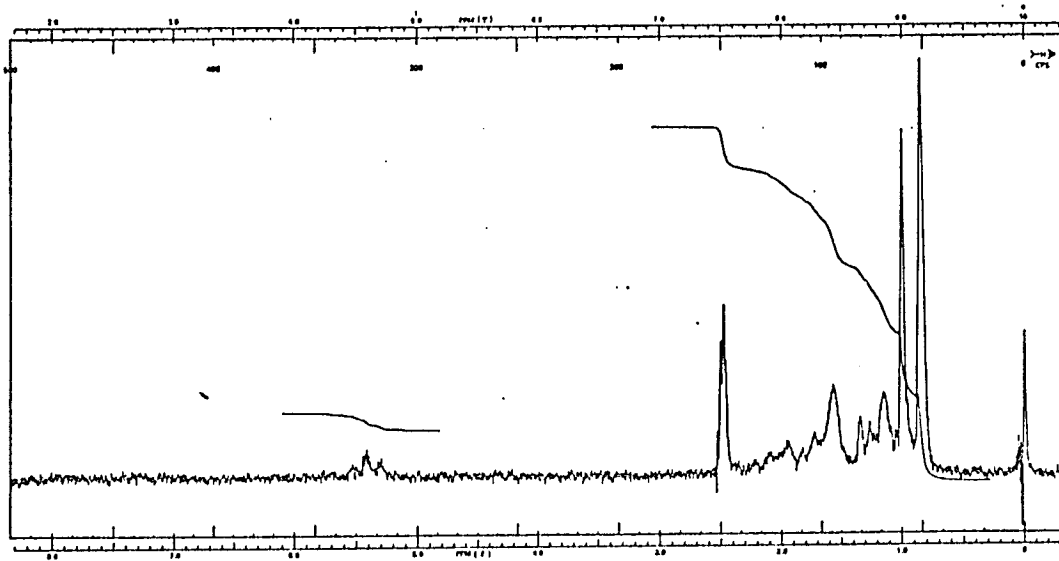
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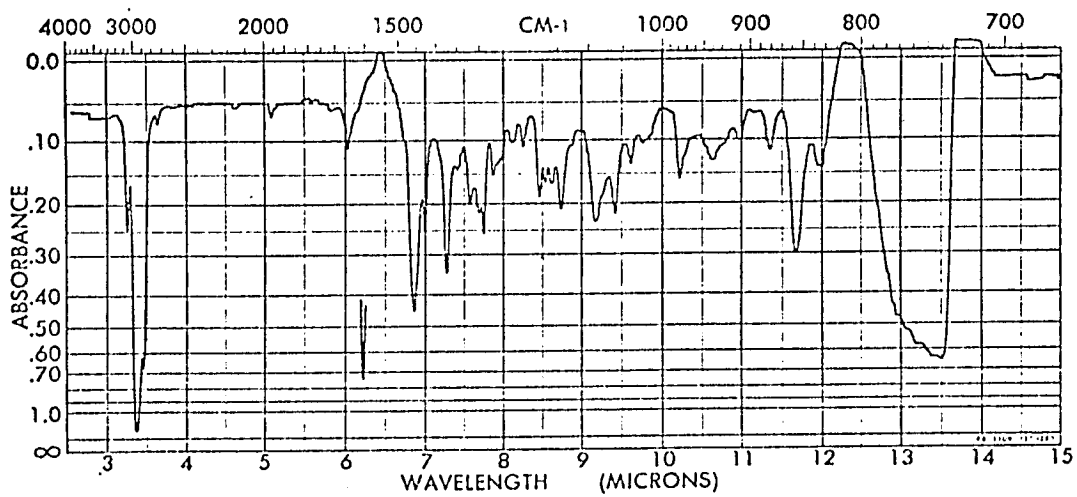
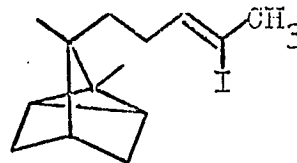


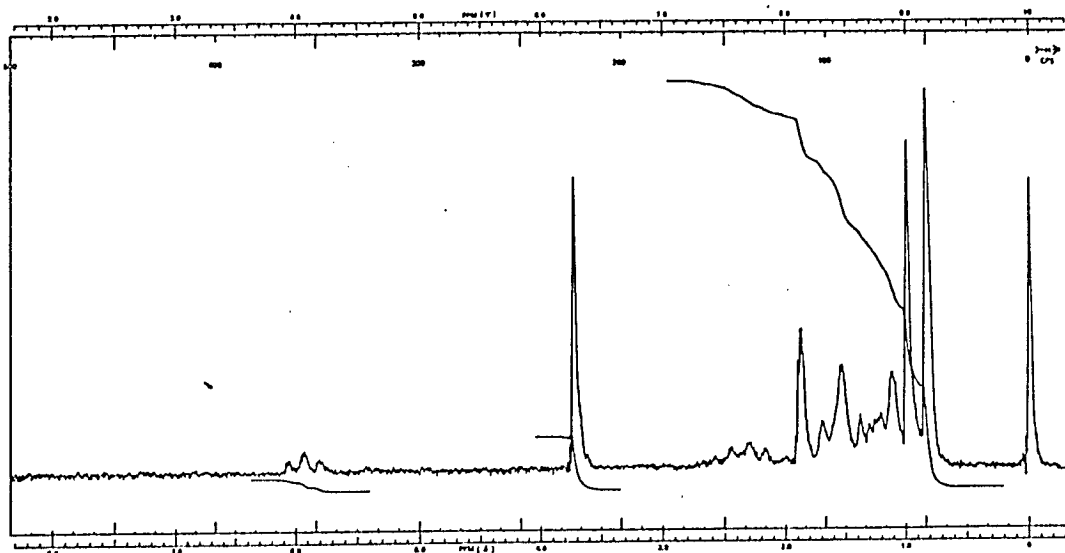
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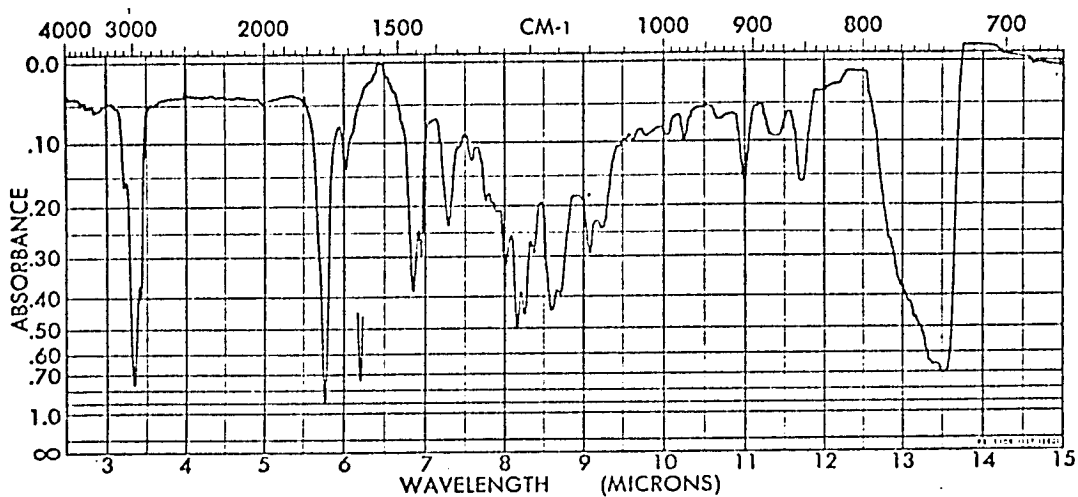
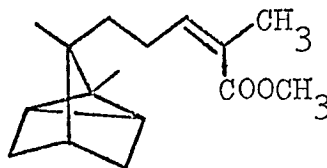


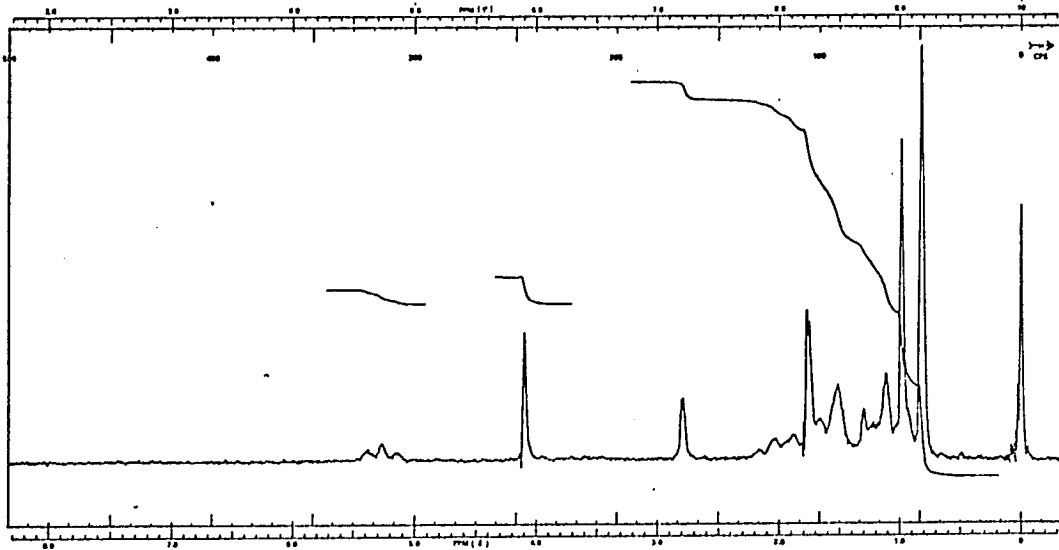
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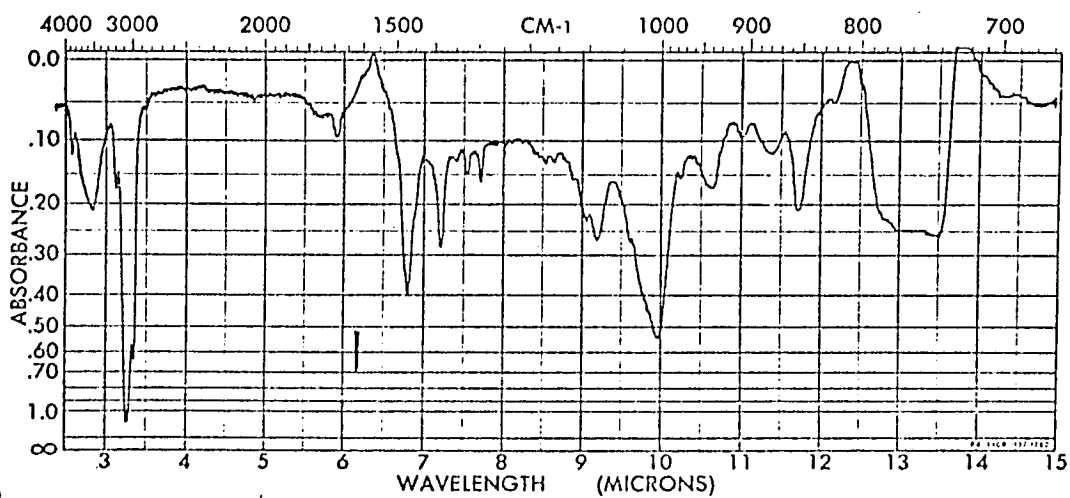
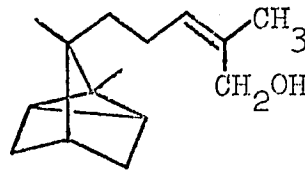


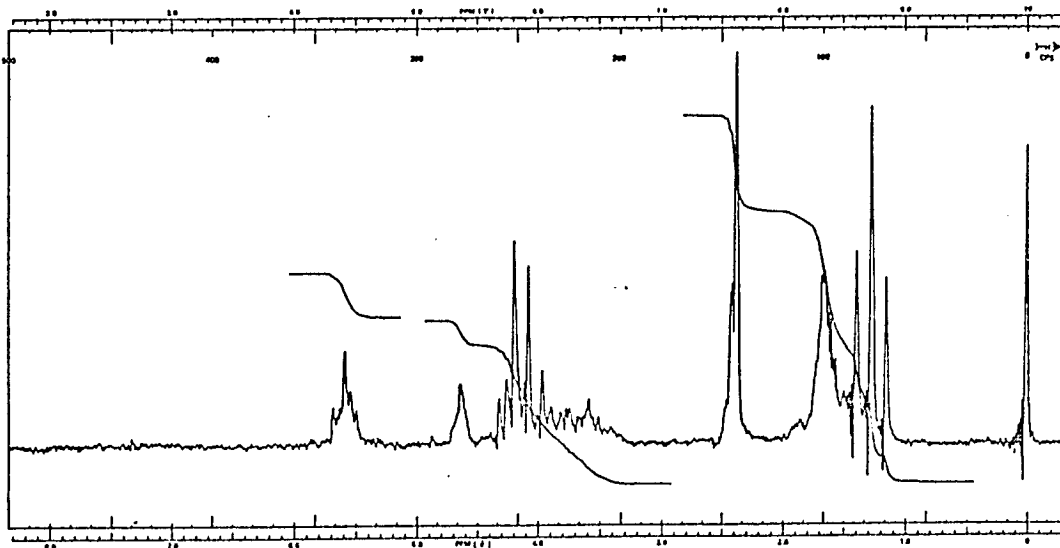
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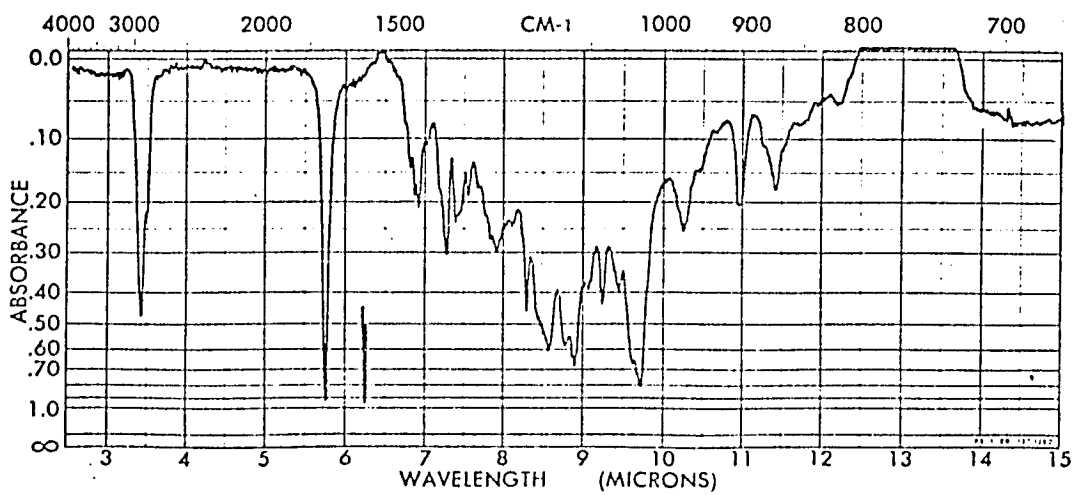
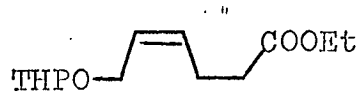


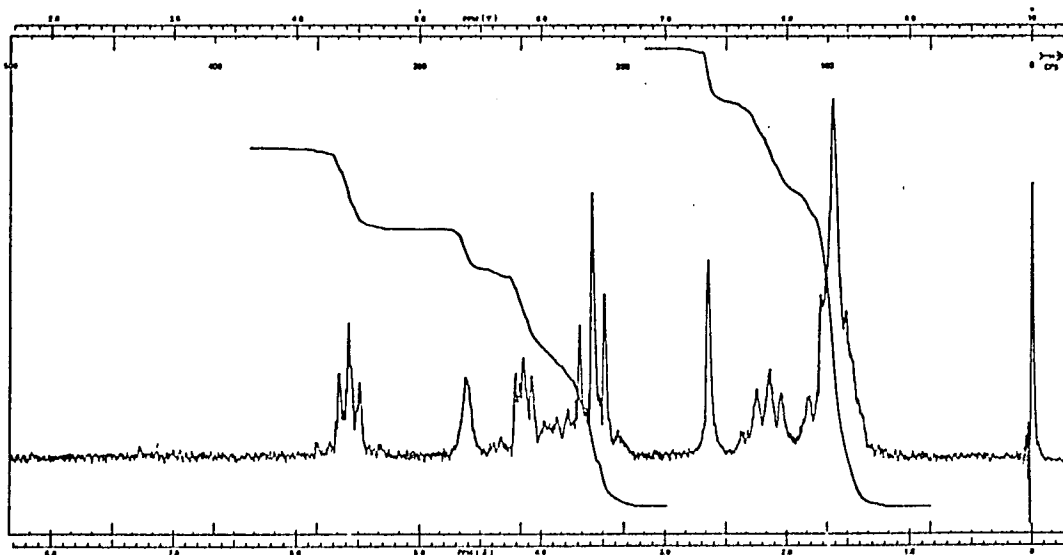
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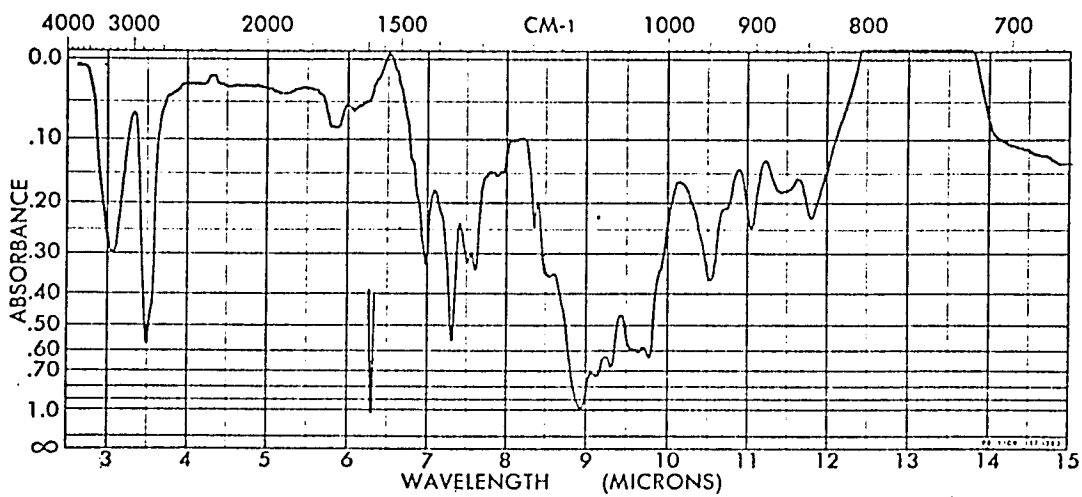
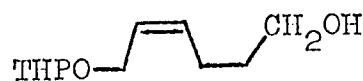


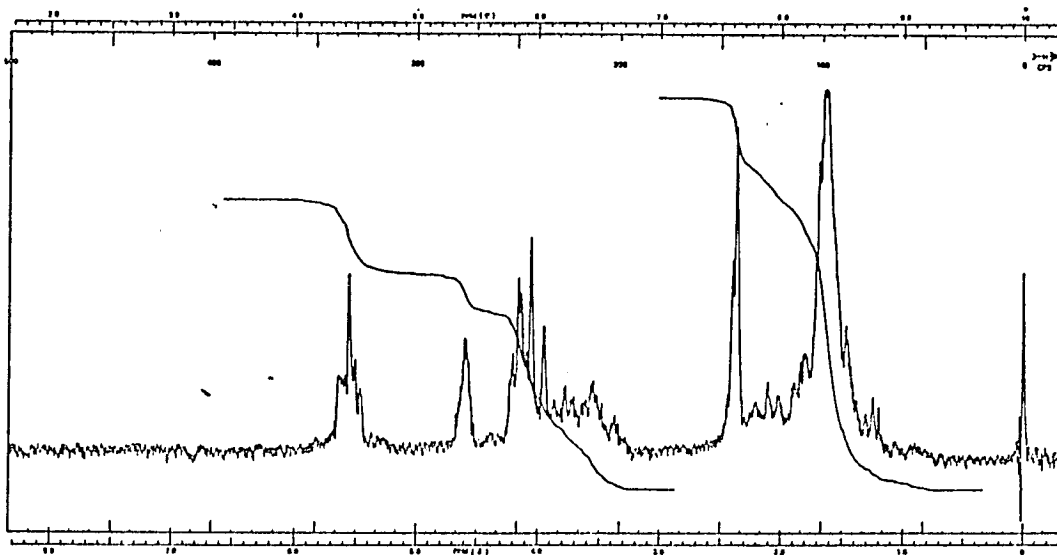
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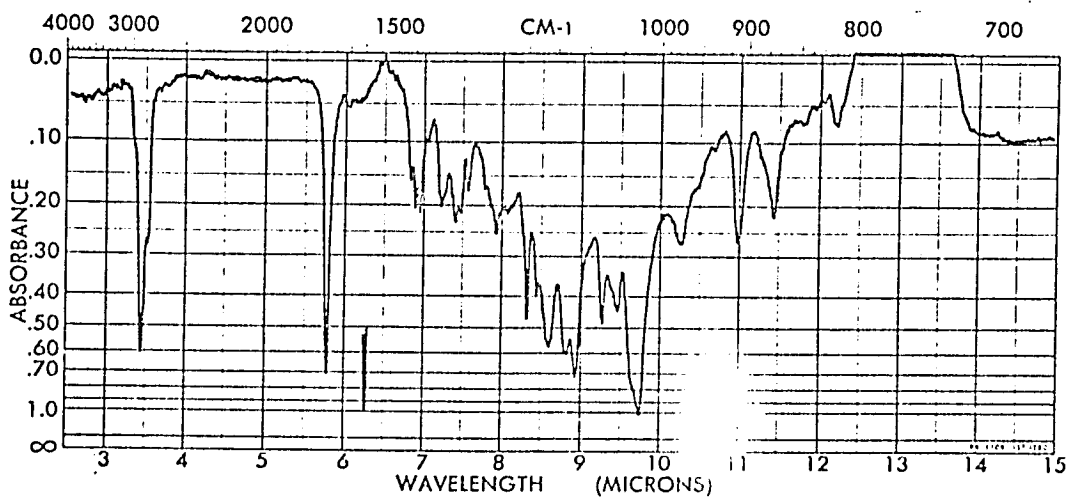
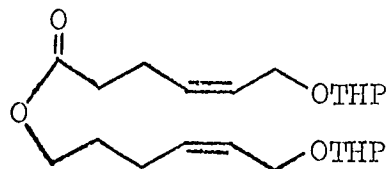


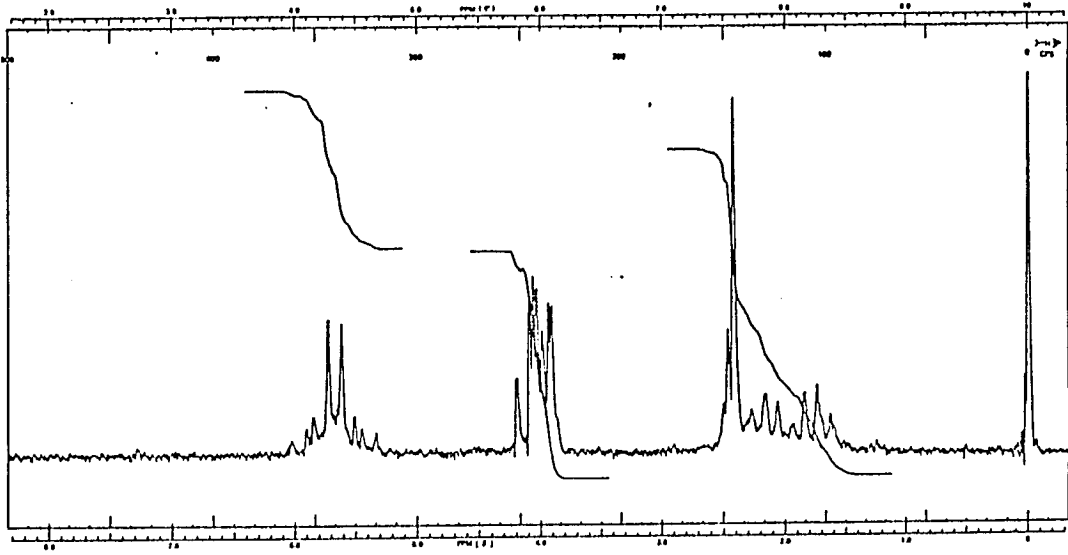
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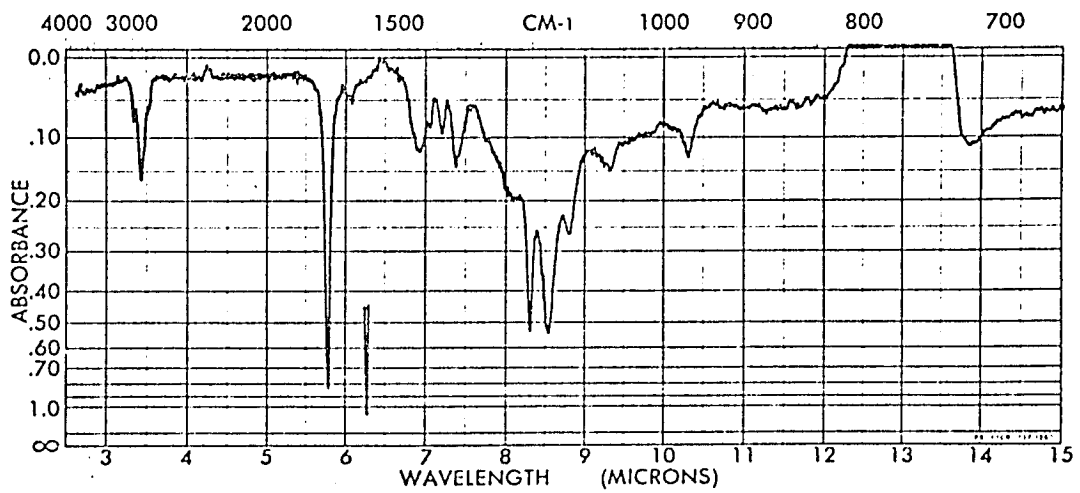
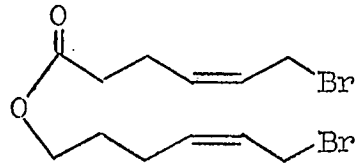


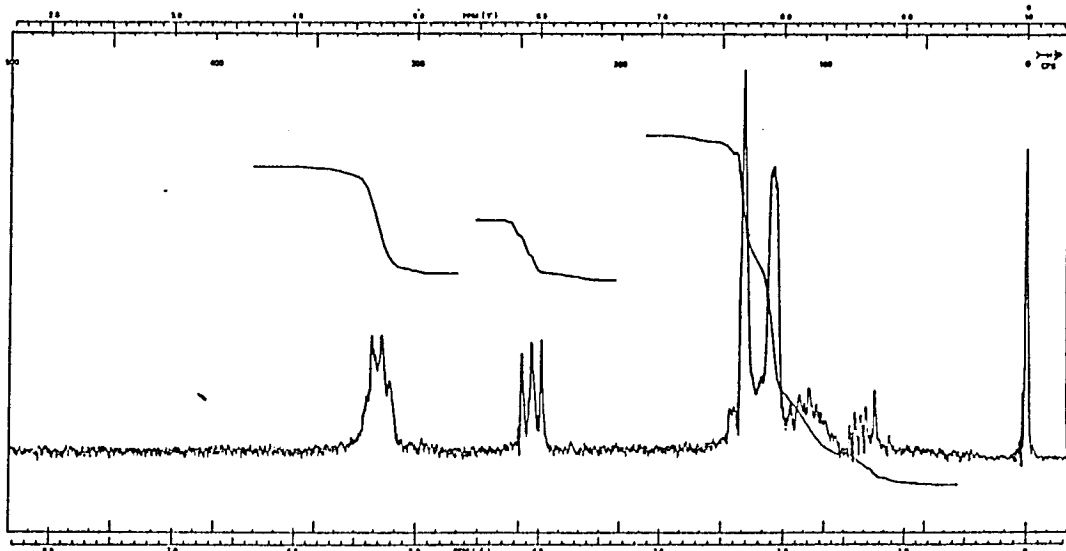
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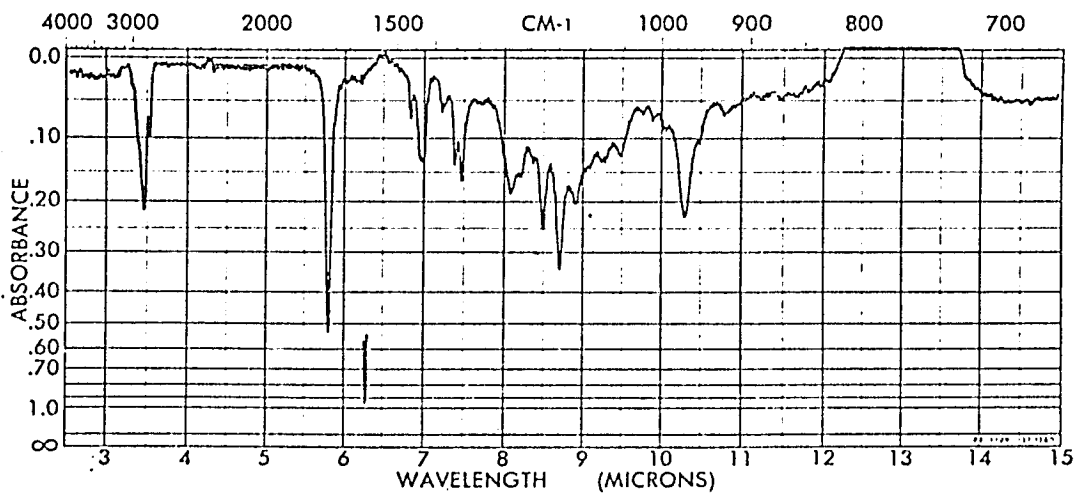
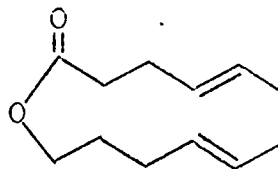


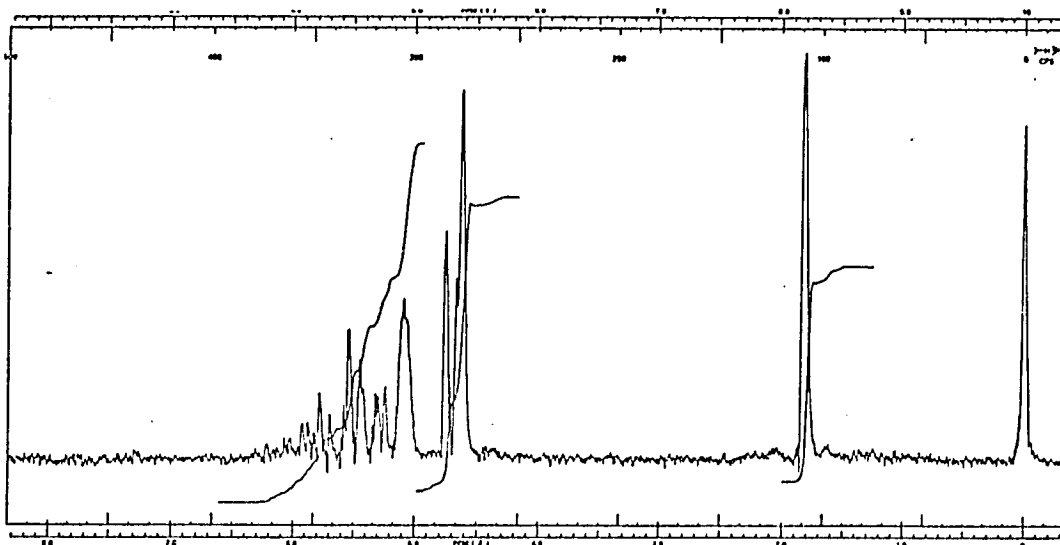
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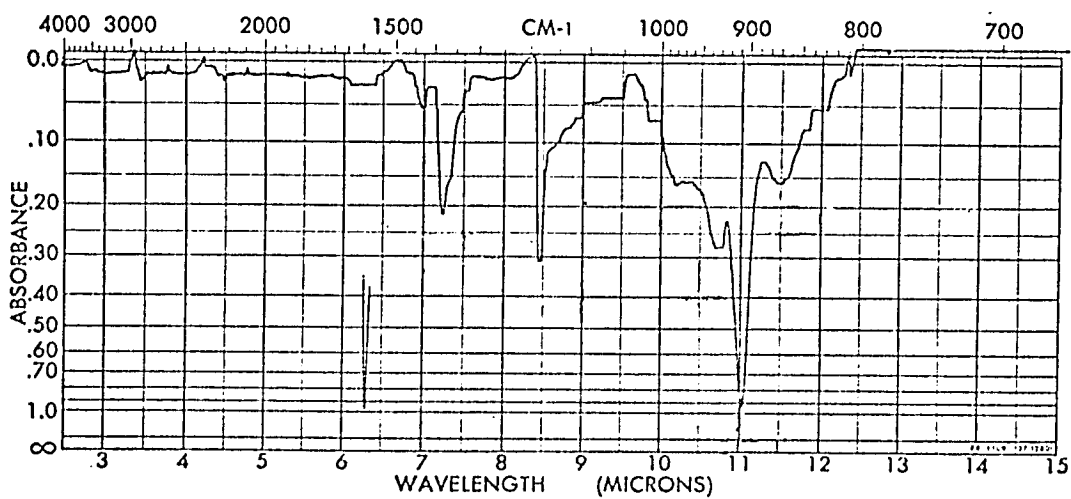
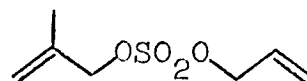


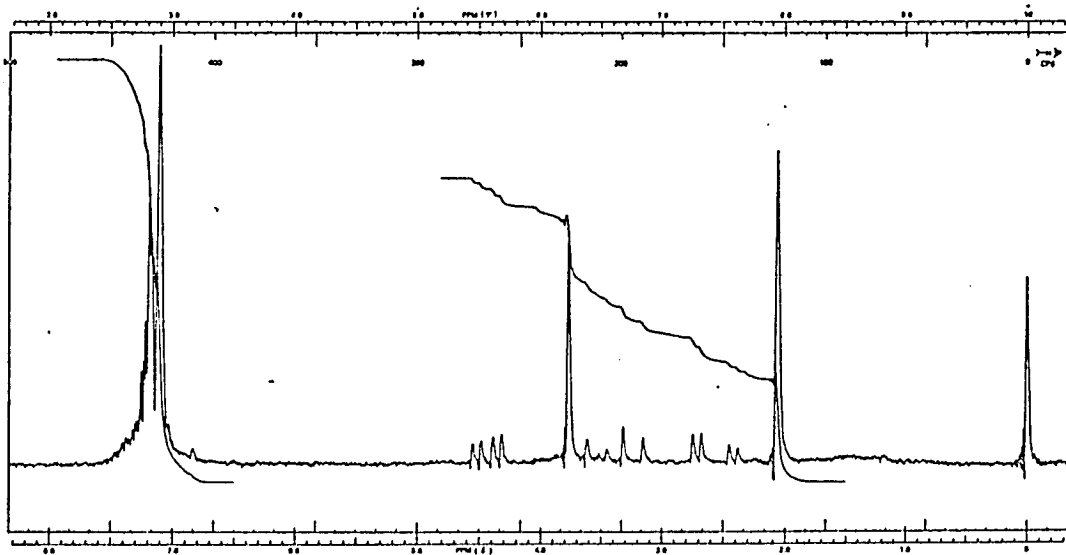
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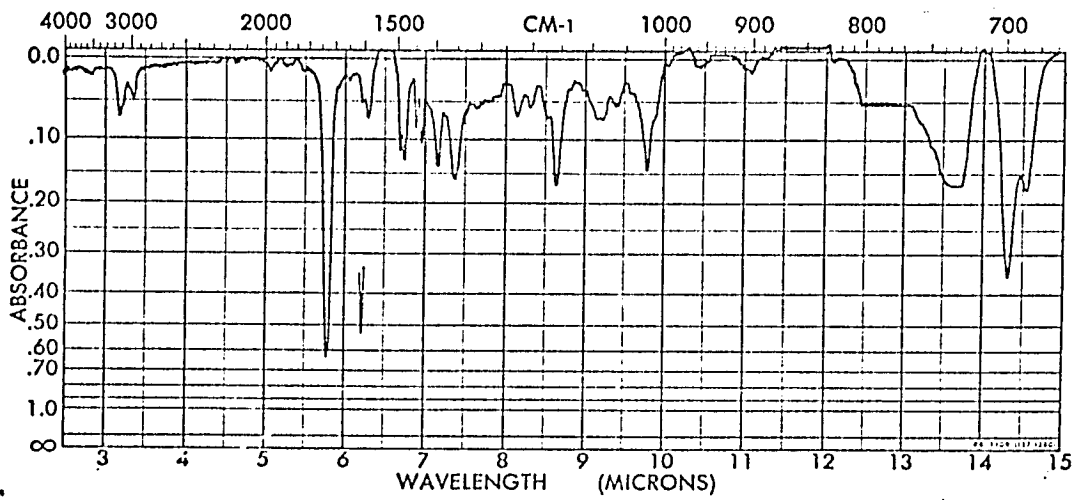
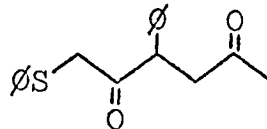


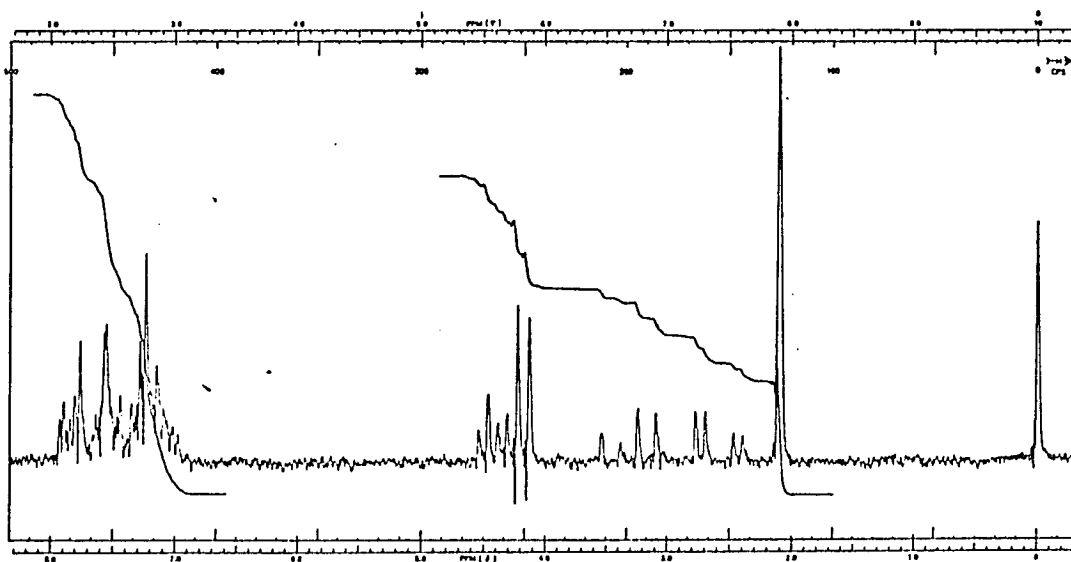
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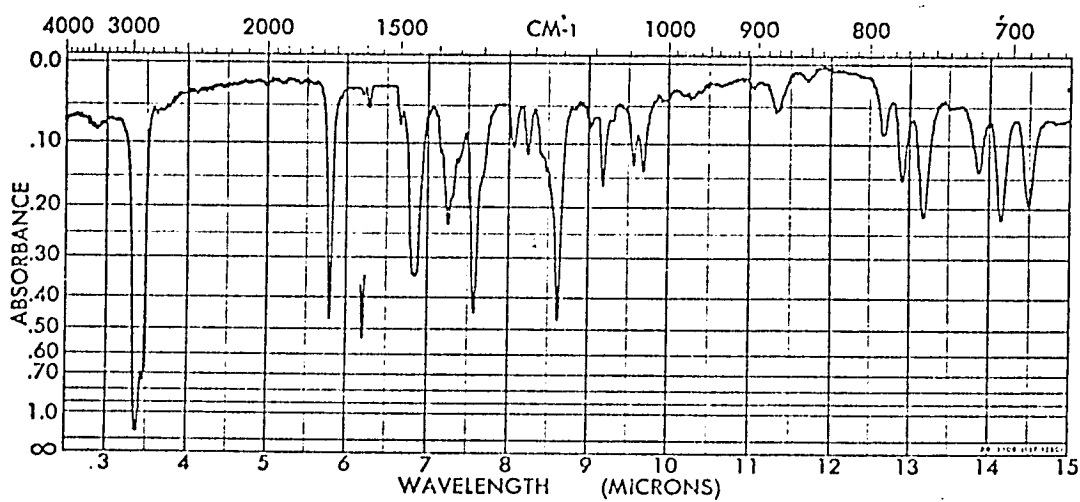
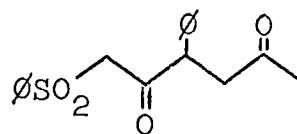


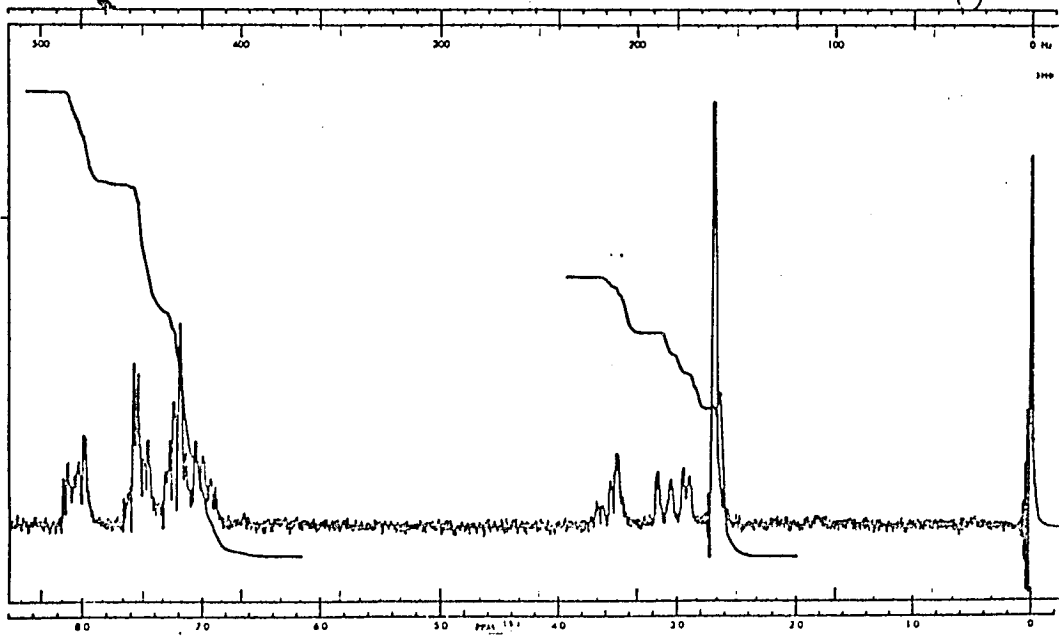
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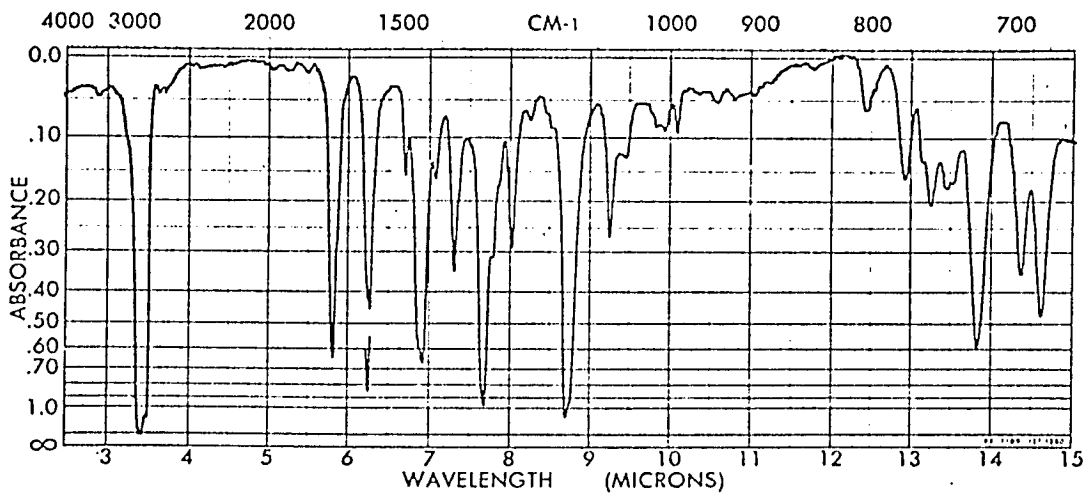
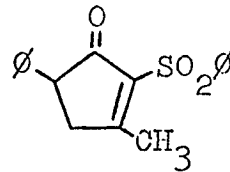


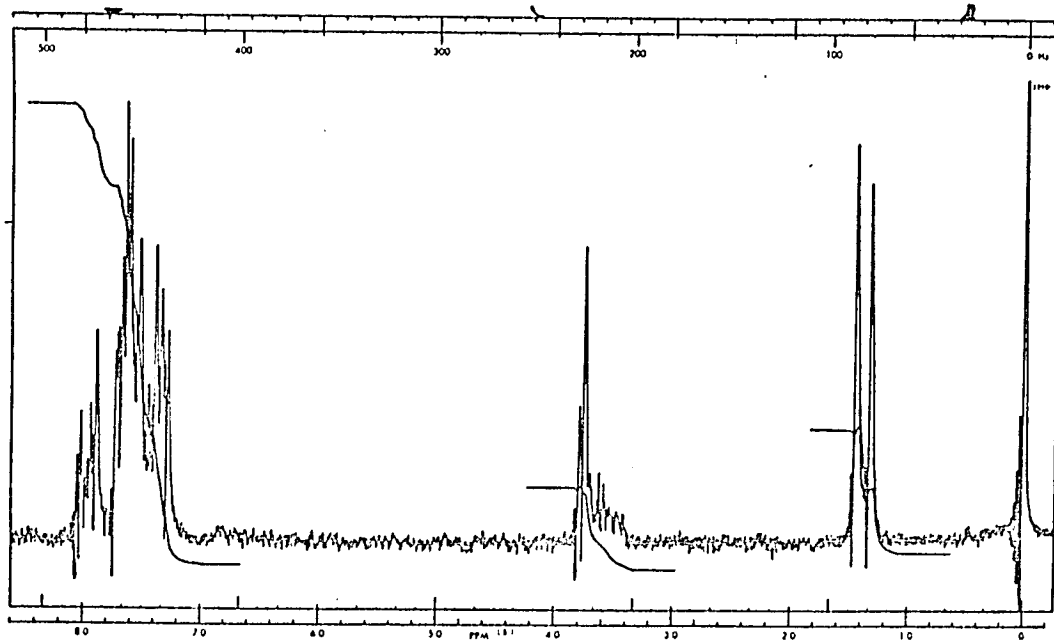
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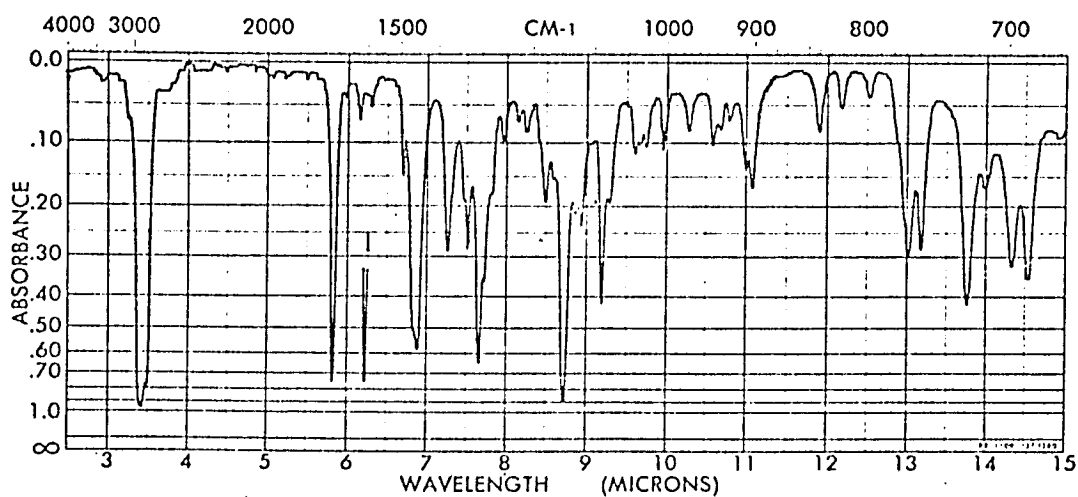
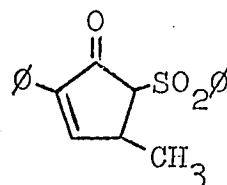


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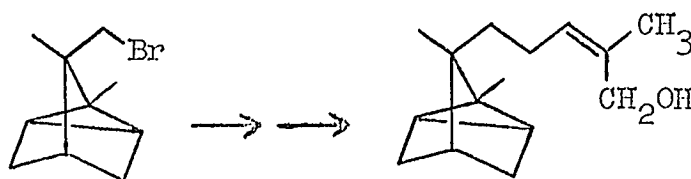
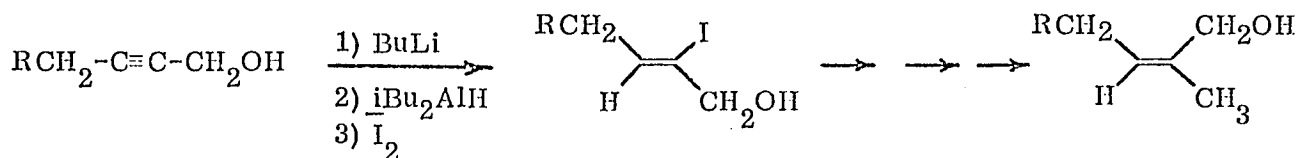
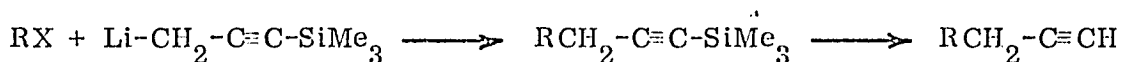
NEW APPLICATIONS OF ORGANOMETALLIC REAGENTS IN ORGANIC SYNTHESIS.
A STEREOSPECIFIC TOTAL SYNTHESIS OF α -SANTALOL

(Summary of Thesis)

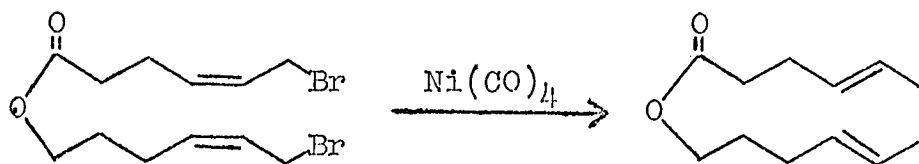
Research Director
Professor E. J. Corey

Herbert A. Kirst
November, 1971

Position-specific propargylation with lithio-1-trimethylsilylpropyne has been developed as a new method for preparing terminal acetylenes and 1,5-dienes. Lithium salts of propargylic alcohols have been reduced stereo- and position-specifically by diisobutylaluminum hydride to yield 2-iodo-trans-allylic alcohols after iodination, and the conversion of these iodoalcohols to 2-methyl-cis-allylic alcohols has been accomplished. These new methods for preparing trisubstituted olefins have been exemplified in a stereospecific synthesis of α -santalol from π -bromotricyclene.



A new route to macrocyclic lactones has been demonstrated by intramolecular cyclization of an α, ω -diallylic bromide with nickel carbonyl.



Studies on the conversion of diallylic sulfates to 1,5-hexadienes by nickel carbonyl and conjugate addition to enones by complexes from nickel carbonyl and anions derived from phenyl methyl sulfide and phenyl methyl sulfone are also described.